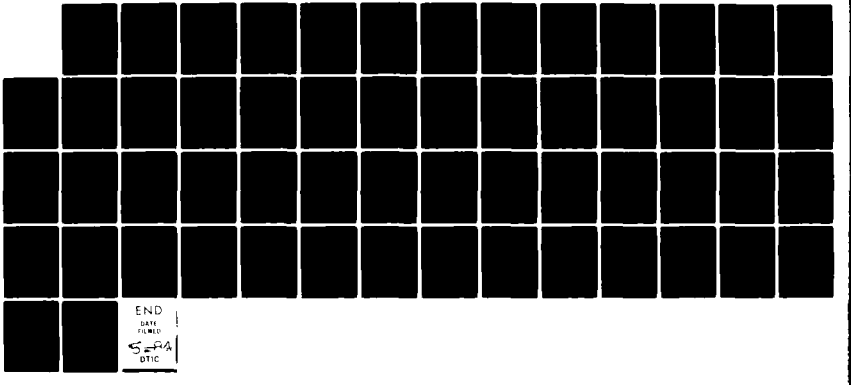
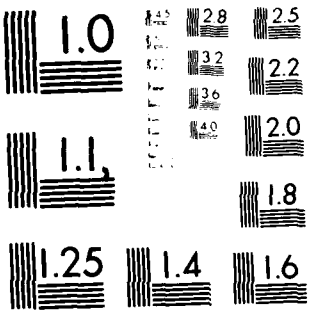
AD-A139 568 POTENTIAL ANTAGONIST OF FOLIC ACID METABOLISM AS MALARIAL DRUGS(U) BISHOP COLL DALLAS TEX J W JONES ET AL. SEP 82 DADA17-72-C-2172 1/1

UNCLASSIFIED F/G 6/15 NL



END
DATE FILMED
5-83
DTIC



AD _____ (1)

FINAL REPORT

POTENTIAL ANTAGONIST OF FOLIC ACID METABOLISM AS MALARIAL DRUGS

Submitted by

Jesse W. Jones and Robert Masingale, Sr.

SEPTEMBER 1982

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701

Contract No. DADA17-72-C-2172

Bishop College
Dallas, Texas 75241
(214) 372-8768

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A139	3. RECIPIENT'S CATALOG NUMBER SCL
4. TITLE *(and Subtitle)* POTENTIAL ANTAGONIST OF FOLIC ACID METABOLISM AS MALARIAL DRUGS		5. TYPE OF REPORT & PERIOD COVERED Final
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Jesse W. Jones and Robert Masingale, Sr.		8. CONTRACT OR GRANT NUMBER(s) DADA17-72-C-2172
9. PERFORMING ORGANIZATION NAME AND ADDRESS Bishop College Dallas, Texas 75241		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62759A.3A762759A829.00.043
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command ATTN: SGRD-RMS Fort Detrick, Frederick, MD 21701		12. REPORT DATE Sep 1982
		13. NUMBER OF PAGES 56
14. MONITORING AGENCY NAME & ADDRESS(*if different from Controlling Office*)		15. SECURITY CLASS. *(of this report)* unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT *(of this Report)* Approved for public release; distribution unlimited		
17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*		
20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*		

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

CONTENTS

INTRODUCTION

This research effort was directed toward a general synthesis which embraced the preparation of substances possessing multi-site inhibitory activity. It was reasoned that such species would be more effective and less likely to result in parasitic resistance. Moreover, in an attempt to minimize possible random inhibitory actions, the molecular design incorporated structural features of well studied malarial drugs.

The focal point of attack for drug design in the present investigation was to exploit the known differences of folic acid matabolism in man and the malarial parasite. It was therefore desirable to prepare target compounds in three series of nitrogen heterocycles which (a) retained antifol structural features and (b) incorporated other antimalarial moieties. The three series included are (1) tetraazanaphthalenes, (2) 1,3,5-triazanaphthalenes, and (3) 9-deazapurines.

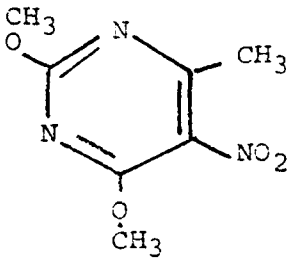
Antimalarial Screening Results

Fourteen (14) samples all of which were intermediates submitted under the contract for screening in mice. These samples represents three (3) types as indicated in Table I. Results from screening indicates that Type I exhibits no apparent antimalarial properties. Type II substances gave indications of some slight though not significant activity. Results from screening of Type III test samples were negative.

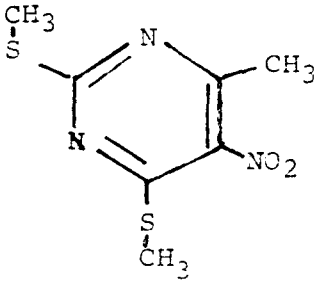
TABLE I A

COMPOUNDS SUBMITTED FOR TESTING

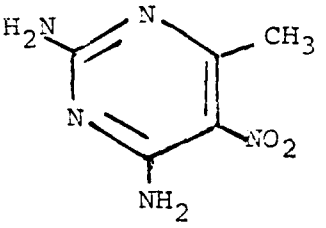
Type I



I-13 BD24384

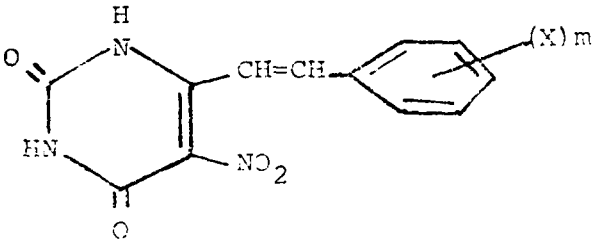


L-120 BC52678

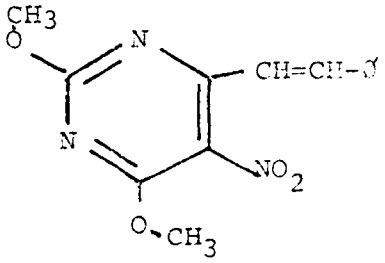


L-126 BC52561

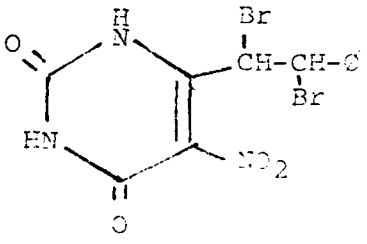
Type II



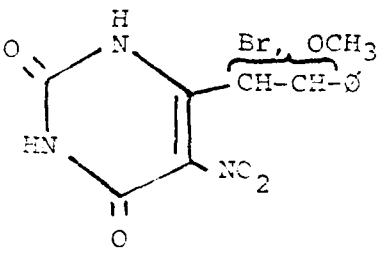
Notebook Ref. No.	WRAIR No.	X/m
N-13	BC52696	null
L-136	BC52552	3-Cl/1
N-26	BD23690	4-F/1
N-27A	BD23707	2,6-Cl/2
N-28	BD23716	2-F/1
N-39	BD23725	2-Cl/1



N-76 BD23743

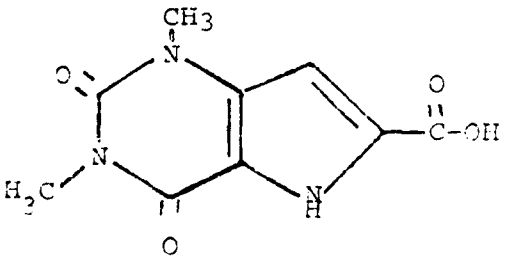


N-44 BD23734

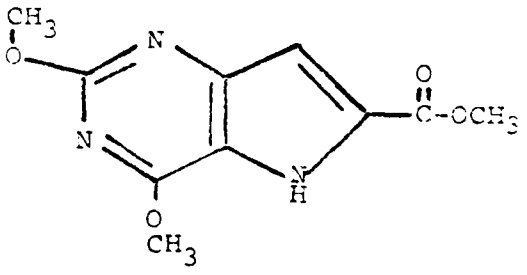


L-126 BC5261

Type III



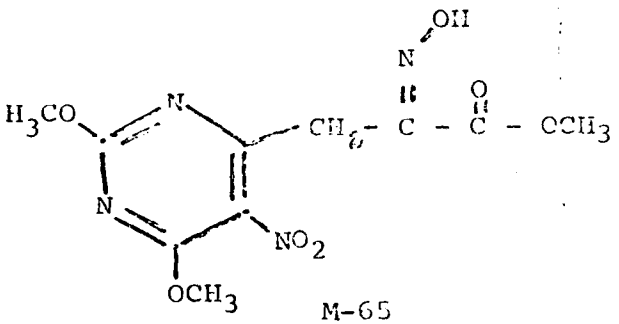
I-41 BD24400



I-38 BD24393

TABLE IB

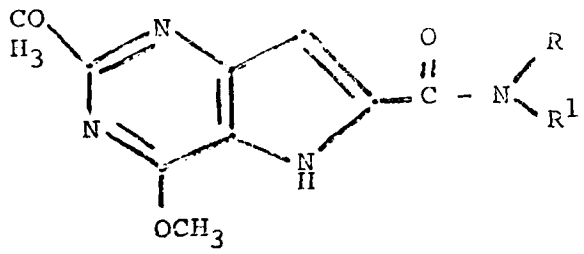
COMPOUNDS SUBMITTED FOR TESTING



M-65

	R	R^1
M-60	H	$\begin{matrix} H \\ H \end{matrix}\!\!>\!C\!=\!CH\!-\!CH_2$
M-61	H	$CH_3(CH_2)_2-$
M-62	$HO-CH_2CH_2-$	$HO-CH_2CH_2-$

(4)



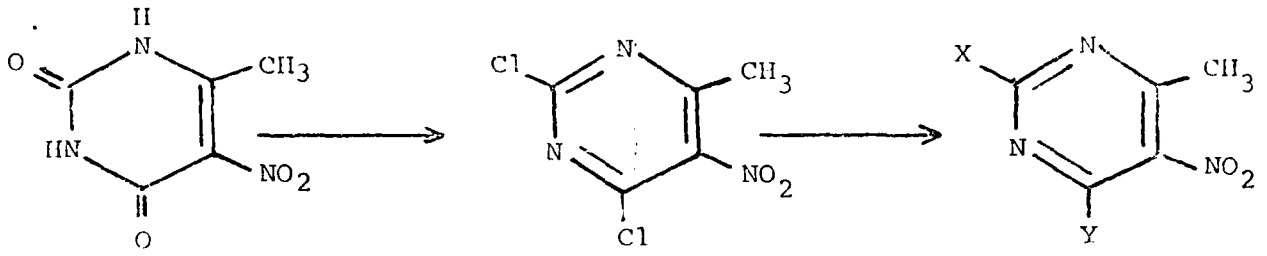
M-60 - M-62

NARRATIVE SUMMARY

Reaction Schemes I and II outlines the progress toward the synthesis of the tetraazanaphthalenes. The initial step involved the condensation of 6-methyluracil (I) with aryl aldehydes in pyridine to give the corresponding 1-(5-nitro-6-uracilyl)-2-arylethene (N-13, AR = Ø). The general application of this reaction permitted the preparation of a number of such derivatives with various substituted aryls. Table II summarizes the physical data collected for the ethenes containing the following aryls: 3-chlorophenyl (L-136), 2,6-dichlorophenyl (N-27), 3,4-dichlorophenyl (N-27), 2-fluorophenyl (N-28), 3-fluorophenyl (N-16) and 4-fluorophenyl (N-26).

Two routes were explored for the synthesis of the 1-(-5-amino-6-uracilyl)-2-arylethynes which are key intermediates in the preparation of tetraazanaphtalenes. The more attractive route led to the bromination of N-13 (AR = Ø) in methanol to give the 1 or 2-bromo-1 or 2-methoxy-1-(5-nitro-6-uracilyl)-2-aryl ethane (N-67). This product was treated with alcoholic potassium hydroxide and gave the corresponding ethyne (N-19). The low percentage yield of N-19 led to efforts to prepare the 1,2-dibromo derivative for subsequent dehydrohalogenation to N-19.

Reaction Scheme I

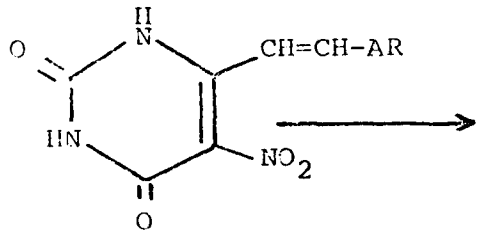


I

II

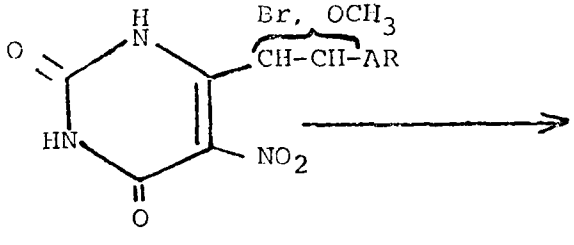
III

III	
I-120:	X, Y = SCH_3
I-124:	X, Y = NH_2
I-13:	X, Y = OCH_3



N-13
(AR = Ø)

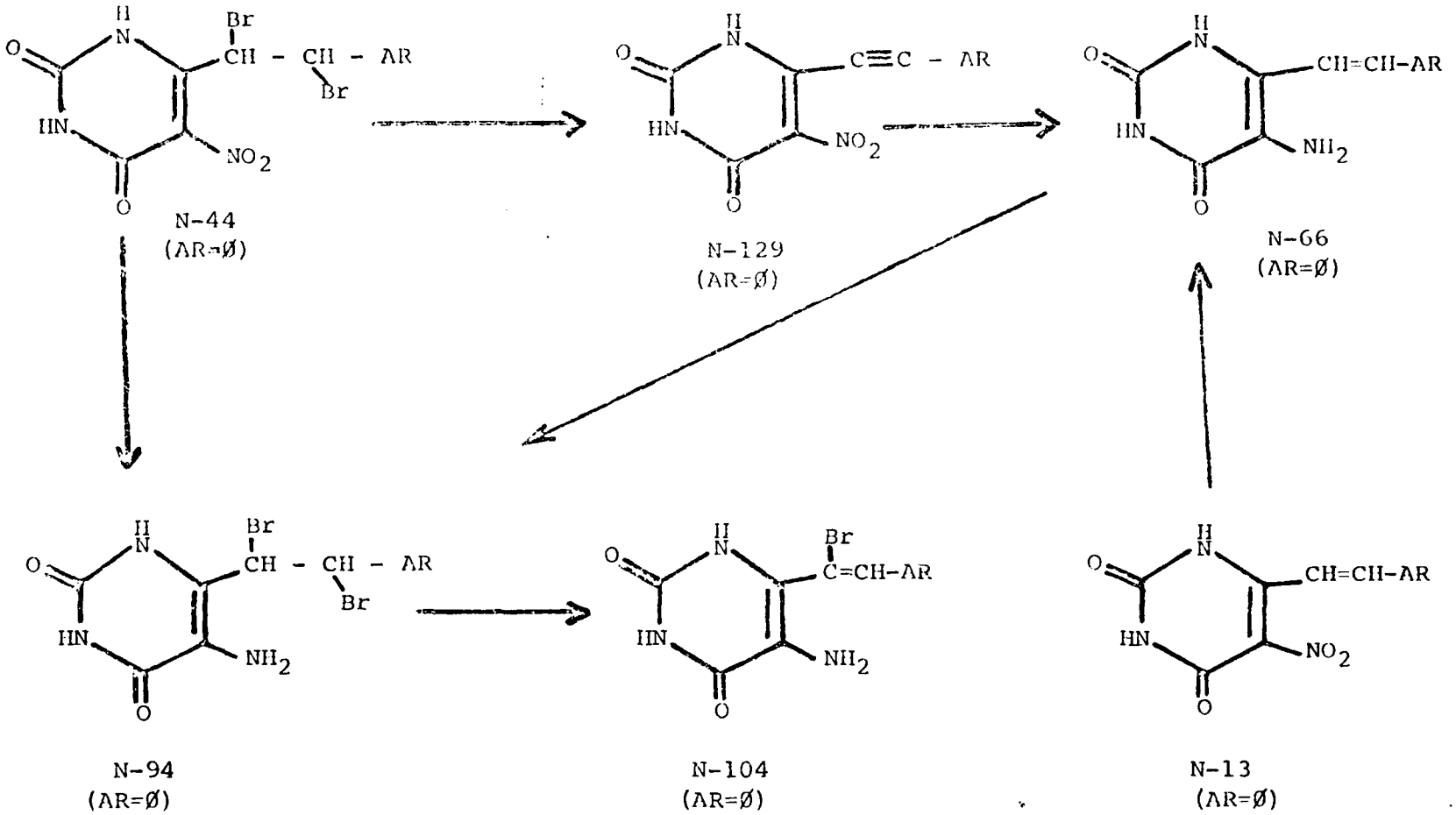
N-44
(AR = Ø)



N-67
(AR = Ø)

N-129
N-19
(AR = Ø)

Reaction Scheme II



(I)

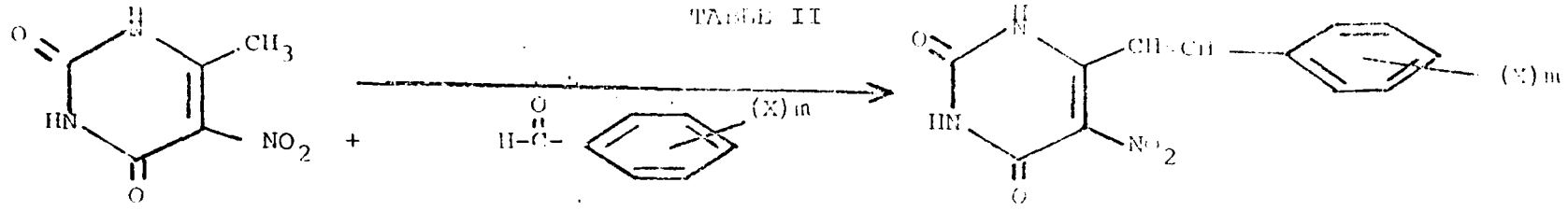


TABLE II

Book No. Empirical Formula	X/m	Calculated C	H	N	Found C	H	N	U.V. (λmax) pH 11	pH 1.7	Yield %	R_f Acid	Base	M.P.
N-30 $C_{12}H_8N_3O_4Cl$	2-Cl/1	49.02	2.73	14.25	49.01	2.94	14.06	286	226 287	80	.01	.13	262-265°
L-136 $C_{12}H_8N_3O_4Cl$	3-Cl/1	47.35	2.95	13.09	47.81	2.92	13.98	266	299 268	88	.90	.86	263-265°
N-13 $C_{12}H_9N_3O_4$	Null	55.50	3.47	16.21	55.73	3.26	16.33	285	287 331	75	.72	.47	262-265°
N-16 $C_{12}H_8N_3O_4F$	3-F/1	51.90	2.8	15.1				285	322 285	80	.90	.83	312-314°
N-26 $C_{12}H_8N_3O_4F$	4-F/1	50.25	3.12	14.70	50.19	3.08	14.43	285	325 280	63	.80	.90	314-316°
N-27A $C_{12}H_7N_3O_4Cl_2$	2.6-Cl/2	39.50	3.02	11.49	39.45	2.38	11.52	280	320 280	76	.80	.86	258-260°
N-28 $C_{12}H_8N_3O_4F$	2-F/1	52.00	2.89	15.15	51.71	3.09	15.09	282	282	78	.80	.86	308-310°
N-29 $C_{12}H_7N_3O_4Cl_2$	3 4-Cl/2							290	331 285	89	.81	.87	320-322°

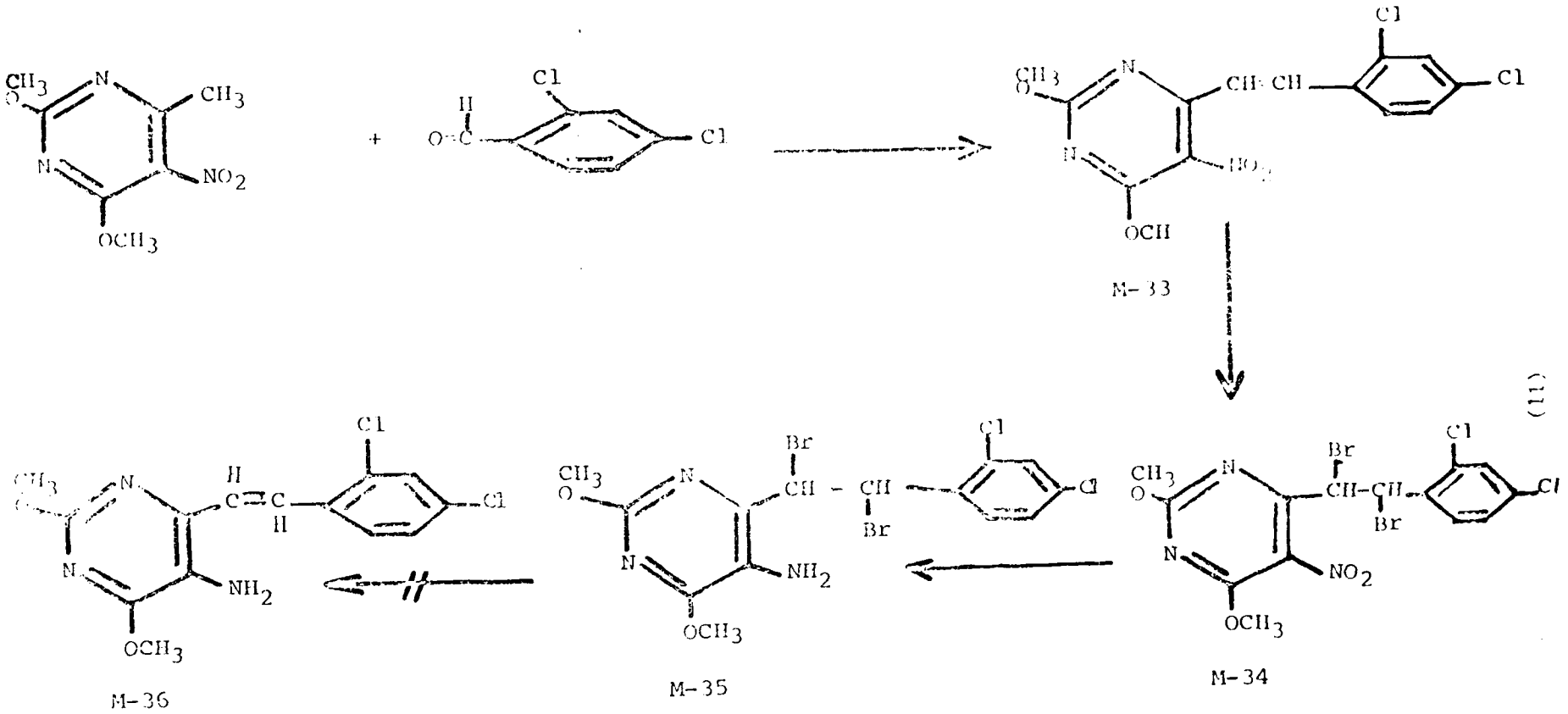
5-Nitro-6-styryluracil (N-13) was brominated in acetic acid to give 1,2-dibromo-1-(5-nitro-6-uracilyl)-2-phenylethane (N-44). When N-44 was treated in refluxing 5% alcoholic potassium hydroxide, the corresponding ethyne (N-129) was isolated. This product (N-129) was indentical to N-19 which was prepared by the action of alcoholic potassium hydroxide on 1 or 2-bromo-1 or 2-methoxy-1-(5-nitro-6-uracilyl)-2-phenylethane. With this structure firmly established efforts were undertaken to selectively reduce the nitro group in the presence of the ethyne group. A variety of reducing agents were used including Raney nickel (N-96), sodium hydrosulfite (K-236) and sodium sulfide (K-237). In no instance was there an indication of the retention of a triple bond as judged by careful examination of infrared spectral data of all solid fractions. The mildest procedure (K-237) gave a product indentical to 5-amino-6-styryluracil (N-66).

An obvious alternative in view of the above described problem was to synthesize a derivative which did not require reduction subsequent to the formation of the triple bond. Consequently, 1,2,-dibromo-1-(5-amino-6-uracilyl)-2-phenylethane (N-94) was prepared from N-66 by bromination in acetic acid. Reduction of N-44 was also achieved by reaction in the presence of Raney Nickel catalyst (N-85), however, the low solubility of N-44 in methanol resulted in a considerable amount of

unreacted material which was difficult to separate. When N-94 was treated with alcoholic potassium hydroxide a product was isolated that contained a halogen and exhibited an ultra violet spectra similar to 5-amino-6—styryl uracil. Moreover, no evidence of a triple bond was present. This evidence suggested that the 5-amino group deactivates carbon-1 toward dehydrohalogenation. Reaction scheme III outlines a route which should minimize this effect in much the same manner as observed in the fascile condensation of 2,4-dimethoxy-5-nitro-6-methylpyrimidine (I-13) and dietyloxalate but not with 5-nitro-6-methyluracil. The condensation of I-13 with aryl aldehydes proceeded readily in sodium methoxide to give the expected 1-(2,4-dimethoxy-5-nitro-6-pyrimidyl-2-arylethene (N-76, AR = phenyl; M-33, AR = 2,4-dichlorophenyl). Bromination of M-33 gave the expected dibromoethane (M-34) which was reduced in the presence of Raney Nickel to give the corresponding 5-amino derivative (M-35). Treatment of M-35 with alcoholic potassium hydroxide apparently gave a 1-bromoethene derivative (M-36) rather than the expected ethyne.

The original synthetic approach suggested that 2,6-dimethylthio-5-nitro-6-methylpyrimidine (L-120) be employed as a major intermediate in the preparation of 9-deazapurines. The inability to perfect condensation of the dimethylthio derivative (L-120) with diethyloxalate led to the selection and preparation of 2,6-dimethoxy-5-nitro-methylpyrimidine (I-13). Condensation of I-13 with diethyl oxalate in the presence of sodium methoxide gave the expected product (I-27) except that the ester alkyl group underwent an exchange reaction in the presence of excess sodium methoxide. The preparation of the desired 9-deazapurine (I-38)

Reaction Scheme III



M-33

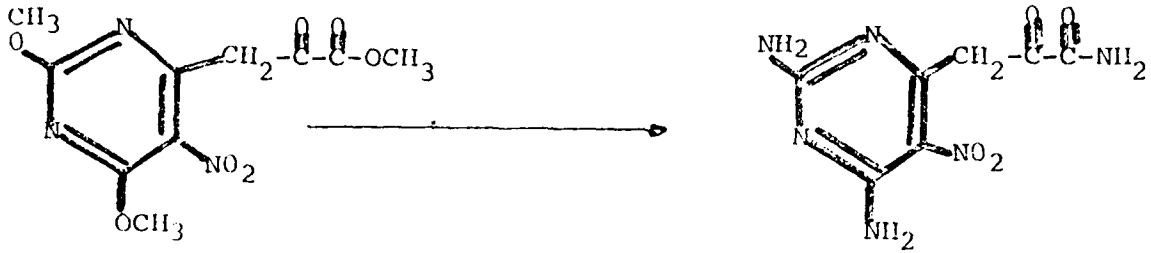
M-34

M-35

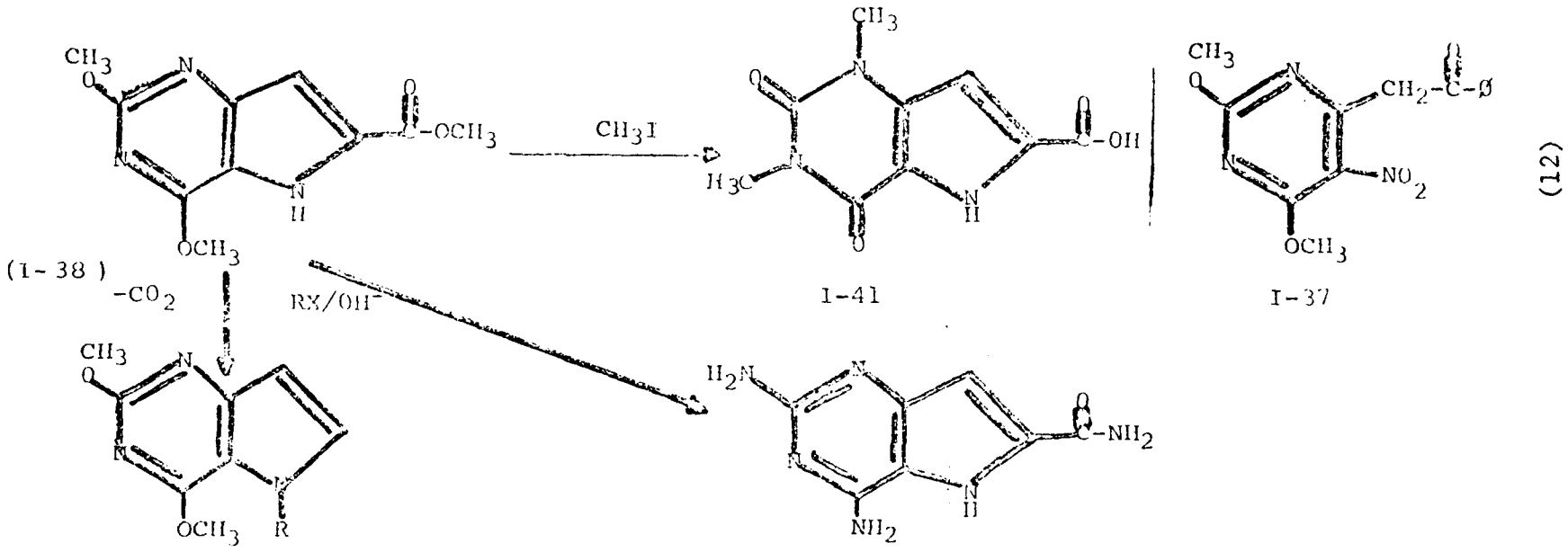
M-36

(II)

Reaction Scheme IV



I-69 I-76



(I-38) I-41 I-37

I-74 R (CH_3)
I-72 (R allyl)
I-71 (R, benzyl)

I-77

(12)

resulted from zinc-acetic acid reduction of VIII.

The alkylation of 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (I-38) in dimethyl foramide was performed with methyl iodine (I-41) and -chlorotoluene (M-26) to give products which indicates fascile alkylation. In addition to alkylation, the methoxy groups were apparently cleaved to give the corresponding 8-carboxyl—9—deazaxanthine. The ease of cleavage of the methoxy groups (I-38) was studied further. It was observed that the cleavage was complete within two hours in aqueous hydrochloric acid (refluxing) and within 18 hours in hydroiodic acid at room temperature. In each case 8-carboxyl-9-deazaxanthine (I-40) was isolated. This product (I-40) was confirmed by synthesis from the reduction of 3-(5-nitro-uracilyl)-pyruvic acid (I-39). The latter product (I-39) was obtained as a result of acid hydrolysis (aq. HCl) of 2,4-dimethoxy-5-nitro-6-methoxyalylmethyluracil (M-14-B).

The study of the alkylation of the 9-deazapurines in basic media (aqueous) has led to the isolation of selected 2,6-dimethoxy-7-alkyl-8-methoxy carbonyl-9-deazapurine (I-71, I-72, I-74). It was of interest to compare the alkylation products which resulted from reaction in dimethylforamide (DMF) and in basic media. It was previously noted that evidence suggested that methoxy cleavage occurred in DMF along with alkylation. Whereas in the latter media, simple alkylation occurred as expected along with hydrolysis of the ester group and decarboxylation.

Conditions favorable to the formation of proposed target compounds were developed. (See Reaction Scheme V). When I-38 was treated with the appropriate alkyl or aryl halide in the pre-

sence of potassium carbonate suspended in dimethyl-acetamide (DMAC), the corresponding 7-alkyl or 7-aryl derivative was isolated (i.e. 2-fluoro (I-93), and 4-fluoro (M-29) benzyl, and 3-chloro (M-30) and 2,6-dichlorobenzyl). A similar procedure provided 2,6-dimethoxy-7 glycidolyl-8-methoxycarbonyl-9-deazapurine.

The reaction of ammonia with I-38 under vigorous conditions gave 2,6-diamino-9-deazapurine-8-carboxamide (I-77). Under similar conditions, 3-(2,6-diamino-5-nitro-6-pyrimidyl) pyruvamide (I-76) was obtained from methyl 3-(2,6-dimethoxy-5-nitropyrimidyl) pyruvate (I-69) (Reaction Scheme VI).

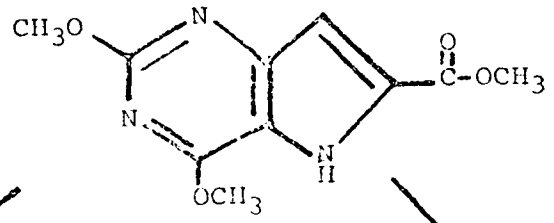
A key intermediate in the synthesis of some 8-aryl-9-deazapurine was also isolated. The condensation of 2, 6-dimethoxy 5-nitro-6-methyl-pyrimidine with methyl benzoate in sodium methoxide gave α-(2, 4-dimethoxy-5-nitro-6-pyrimidyl) acetophenone (I-37).

Reaction Scheme IV outlines the route to several intermediates of interest in the preparation of proposed target compounds. 2,6-Dimethoxy-5-nitro-6-methylpyrimidine (I-13) was readily condensed with ethyl cyanoacetate to give the expected condensate (I-86). This intermediate was required for the preparation of some 8-substitued-9-deazapurines.

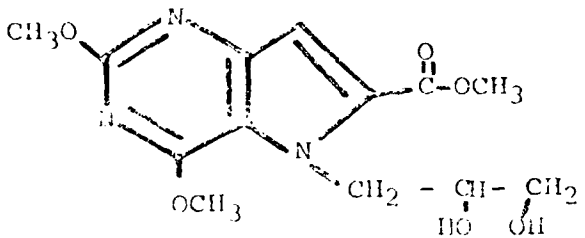
Requisite amide intermediates (I-85) for the preparation of some 8-alkyl carboxamide could best be prepared from I-27 by the reaction of amines in refluxing methanol (Reaction Scheme V).

Certain 9-aryl-9-deazapurines suggested futher synthesis. For example, the isolation of I-27 as a sodium salt suggested the possibility of C-alkylation. Indeed, when 2-fluorobenzylchloride and the I-27 (sodium salt) in methanol were heated under gentle reflux the corresponding 2-fluorobenzyl derivative (I-95) was isolated.

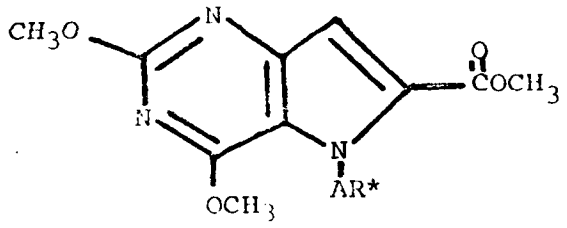
Reaction Scheme V



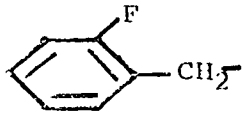
I-38



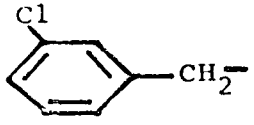
I-84



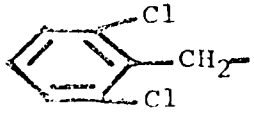
*AR



I-93



M-30



I-91

M-29

(15)

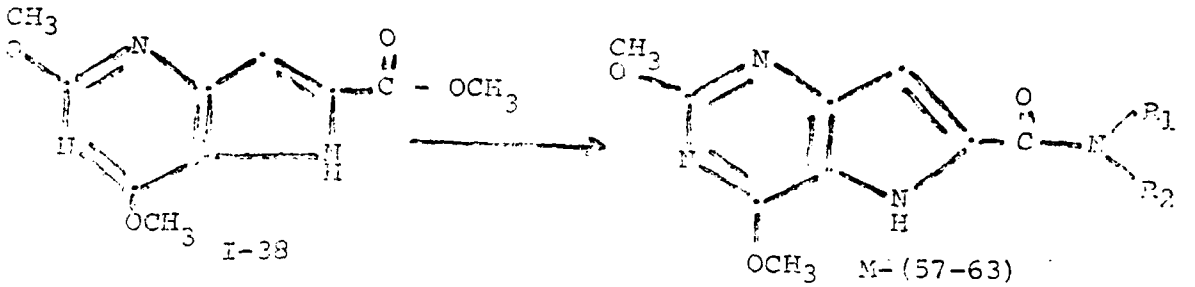
The success of this reaction permitted the synthesis of various-9-aryl or alkyl-9-deazapurines.

The preparation of several carboxamides of 9-deazapurine was accomplished in reasonable yields. The Reaction proceeds under mild reflux temperature with 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (I-38) in methanol containing the appropriate amine. Reaction Scheme I provides a tabular listing of the various amine substituents including examples where R_2 - H and R_1 = benzyl-(M-57), allyl-(M-62) and adamatanyl (M-63).

Efforts were directed toward the synthesis of some 1,3,5-triazanaphthalenes (See Reaction Scheme VII). Ethyl-(2,4-dimethoxy-5-nitro-6-pyrimidyl) pyruvate (I-27) reacts with hydroxylamine to give the corresponding oxime (M-65). The oxime (M-65) was readily reduced with Raney nickel. Chromatograph analysis of the isolated product indicated two products (M-66A and M-66B). Mass spectral studies and NMR analysis of the mixture indicated strong evidence for the structure assigned to M-66B. Indeed when the mixture of M-66A and M-66B was heated in methanol, the latter product increased in concentration. Further purification of M-66B is being undertaken since the possibility exist for a fascile synthesis of the tetrahydra-1,3,5-triazanaphthalene.

Reaction Scheme IX outlines two routes which were investigated for the synthesis of 6,7-disubstituted-1,3,5-triazanaphthalenes. An excellent yield of 2,4-dimethoxy-5-amino-6-methylpyrimidine (AA-26) was obtained when the corresponding 5-nitro derivative (I-27) was treated with aqueous hydrazine. The reaction of AA-26 with benzil (R = Ø) and biactyl (R = CH_3) in refluxing methanol gave the schiff base which was subsequently refluxed in sodium methoxide to give a product tentatively identified as the target compound (R = Ø, M-71).

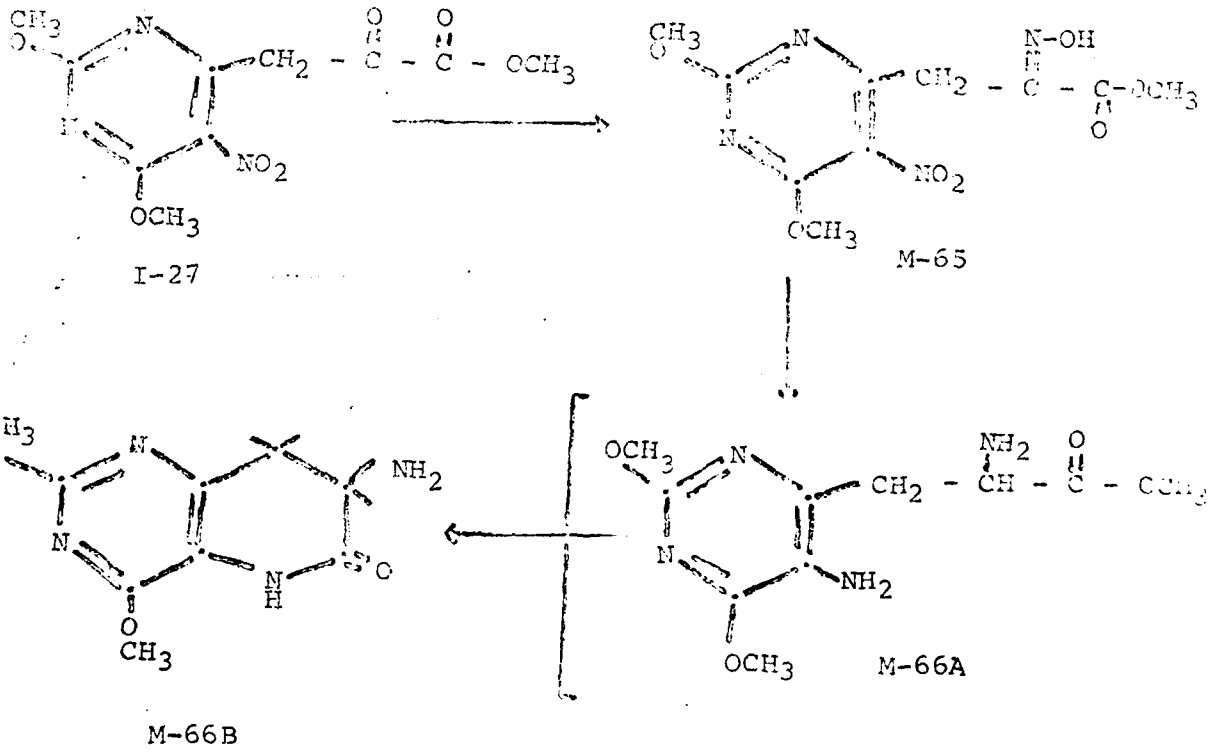
Reaction Scheme VI



I-38 M-(57-63)

	R_1	R_2		R_1	R_2
M-61	$CH_3CH_2CH_2CH_2$	H		$-CH_2CH_2-Cl$	$-CH_2CH_2-Cl$
M-58	$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2CH_2$	M-57	$\emptyset CH_2-$	H
M-59	$CH_3CH_2CH_2$	H	M-60	$CH_2=CH-CH_2-$	H
M-63	1-adamantanyl	H	M-62	$HOCH_2-CH_2-$	$HO-CH_2CH_2-$

Reaction Scheme VII

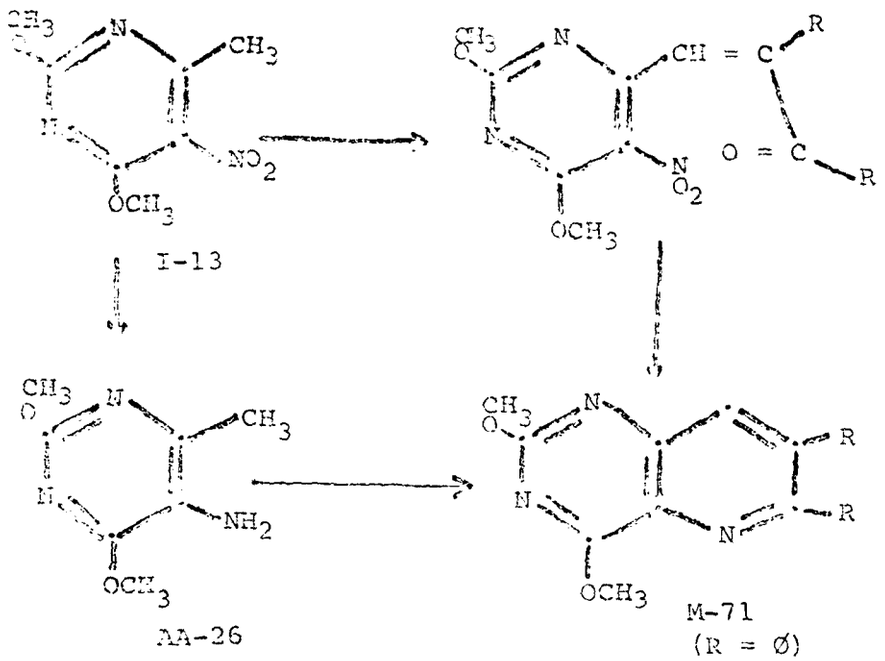


I-27 M-65

M-66A M-66B

The apparent sensitivity of the triple bond in certain 1-(5-nitro-6-uracilyl)-2aryl ethynes resulted in only modest quantities of the requisite 5-amino derivative. Thus, efforts were discouraged to pursue the synthesis of the tetraazanaphthalenes. However, several interesting intermediates were isolated and it was desirable to probe their usefulness as antimalarial types. In this respect, the preparation of several 5-triazinopyrimidines were undertaken (See Reaction Scheme X). The coupling reaction proceeded readily by stirring at room tempearture 1-(5-diazo-6-uracilyl)-2-phenyl-ethene (Q-76) and the appropriate amine. Likewise, when Q-76 was allowed to stir in a methanol solution containing an appropriate mercaptan, the corresponding thiadiazene was isolated.

Reaction Scheme VII

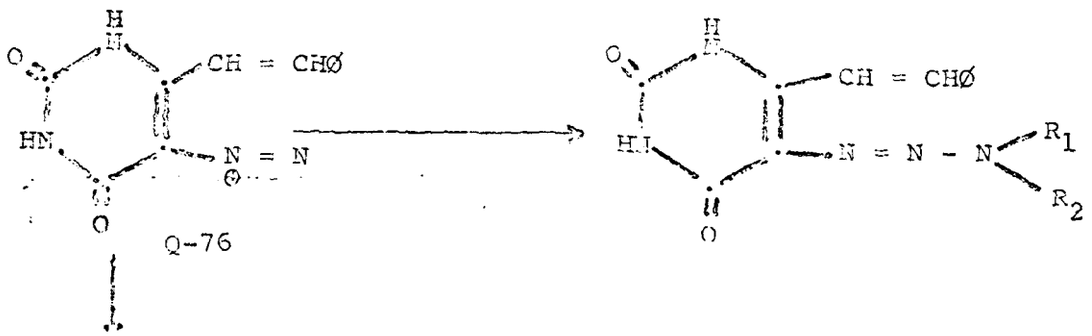


I-13

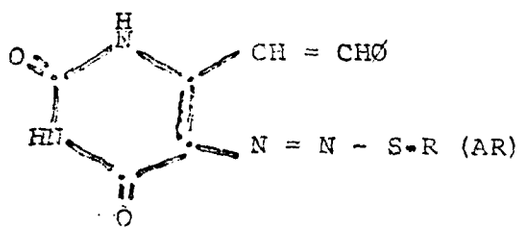
AA-26

M-71
(R = Ø)

Reaction Scheme X



Q-76



BK#1	(R (AR)
Q-77	Ø-
J-123	CH_3CH_2-

BK#	R_1	R_2
Q-81	$-CH_2CH_2OH$	$-CH_2CH_2OH$
Q-79	$-(CH_2)_3CH_3$	$-(CH_2)_3-CH_3$
Q-78	H	$(CH_2)_3CH_3$
Q-84	$-(CH_2)_2Cl$	$-(CH_2)_2Cl$
Q-80	H	Ø $-CH_2-$
Q-82	H	$-CH_2CH_2CH_3$
Q-83	H	$-(CH_2)_5CH_3$

EXPERIMENTAL

The Preparation of 2,4-Dimercapto-5-Nitro-6-Methylpyrimidine (L-199).

Thiourea (7.5 g) was added to 200 ml of methanol while stirring at room temperature. 2,4-Dichloro-5-nitro-6-methylpyrimidine (5.0 g) was then added to the solution which was then refluxed for 2.5 hours, and finally evaporated to dryness. Water (50 ml) was added to the residue, and the product was then filtered and dried to air. The product was crystallized from methanol to give an orange solid, m.p. 200-202 which was homogeneous in two chromatographic solvent systems.

The Preparation of 2,4-Dimethylmercapto-5-Nitro-6-Methylpyrimidine (L-120).

2,4-Dimercapto-5-nitro-6-methylpyrimidine (5 g) was added to 150 ml of 5% sodium bicarbonate while stirring at room temperature. Methyl iodide (10 g) was added, and the mixture was stirred for 2.5 hours. The precipitate which formed was filtered and washed with 50 ml of H_2O. Recrystallization of the product from methanol gave reddish needles, m.p. 47-48°, λ Max. pH 1.7 285; pH 11 289 n.m.. Anal. Calcd. for $C_7H_9S_2O_2$: C, 36.3;H, 3.8,N, 18.1. Found: C, 35.99, H, 4.6; N, 17.92.

The Preparation of 2,4-Diamino-5-Nitro-6-Methylpyrimidine (L-124).

2,4-Dichloro-5-nitro-6-methylpyrimidine (10 g) was dissolved in 300 ml of methanol and allowed to stir at room temperature for 15 minutes. The mixture was then transferred to a 3-necked flask

equipped with a drying tube containing calcium chloride and a thermometer. Ammonia was then allowed to bubble through the reaction vessel for 1 hour at a temperature of 50° - 55°. The reaction flask was then cooled to room temperature, and the precipitate which formed was filtered and washed with H_2O. Recrystallization of the product from methanol gave orange needles (m.p. 228° - 230°), λ Max: pH 1.7 307; pH 11 345 and 254 n.m. Anal. Calcd. for $C_5H_9N_5O_2$: C,35.5; H,4.1;41.4. Found: C, 35.88;H,5.13; N, 42.1.

The Preparation of 2,4,5-Tri-Amino-6-Methylpyrimidine (L-125).

2,4-Diamino-5-nitro-6-methylpyrimidine (5 g) was added to 80 ml of acetic acid while stirring and heating at 70-80°. Zinc (9 g) was then added to the reaction mixture which was stirred for 2 hours at 70-80°. The precipitate which formed was filtered and recrystallized from acetic acid (m.p. 223-225).

Bromination of 5-Nitro-6-Styryluracil (L-126).

Bromine (5 g) was added to 200 ml of methanol while stirring at room temperature. 5-nitro-6-styryluracil (5 g) was then added to the saturated solution and the resulting mixture was stirred for 30 minutes at room temperature. Additional bromine (10 g) was added to dissolve the 5-nitro-6-styryluracil. The reaction mixture was then stirred for an additional 30 minutes. The resulting product was filtered (by gravity) and the solution evaporated to dryness at room temperature. The residue was extracted with water and the aqueous extract bascified with 5% ammonium hydroxide to pH 8. The resulting solid was filtered. The product was purified by dissolving in 50 ml of cold KOH, and neutralized at pH-7 with acetic acid (m.p. 183-185°), λ Max: pH 1.7 386, 273; pH

11 386 n.m. Anal. Calcd. for $C_{13}H_{12}N_3O_5Br$: C, 42.1; H, 3.2; N, 11.3. Found: C, 42.1; H, 3.1; N, 11.1.

The Preparation of 2,4-Dimethoxy-5-Nitro-6-Ethoxalmethylpyrimidine (I-30).

2,4-Dichloro-5-nitro-6-methylpyrimidine was converted in a two step process to 2,4-dimethoxy-5-nitro-6-ethoxalylmethylpyrimidine. The 2,4-dichloro-5-nitro-6-methylpyrimidine (10 g) was dissolved in 100 ml of methanol and the methanolic solution was added to a prepared solution of sodium methoxide (3 g of sodium in 100 ml of methanol). The solution was allowed to stir at room temperature for 30 minutes after which the by product sodium chloride was removed by filtration.

The product in the above solution was assumed to be the desired 2,4-dimethoxy-5-nitro-6-methylpyrimidine. To it was added while stirring at room temperature 10 g of diethyl oxylate and additional sodium methoxide (1 g of sodium in 50 ml of methanol). The solution was allowed to stir for 24 hours. The yellow solid (10 g) was filtered and washed with 300 cc of methanol and dried to air. The product gave a single spot in two solvent systems. The ultraviolet spectra was characteristic of the expected product.

The Preparation of 2,4-Dimethoxy-8-Methoxycarbonyl-9-Deazapurine (I-38).

Reduction of 2,4-dimethoxy-5-nitro-6-ethoxylalmethylpyrimidine (7.2 g) was accomplished in 70 ml of glacial acetic acid with zinc (14 g). The dimethoxy derivative (I-30) was dissolved in acetic acid at 70° while stirring. Zinc was then added carefully while at 70°-80°C. The mixture was stirred for two (2) hours without further

heating. The product was then filtered and the filtrate evaporated to dryness. The residue was azetroped three times with 200 ml of acetone. The residue was then suspended in 100 ml of water and then the mixture was neutralized with 5% Na^4CO_3 to pH 7. The product was filtered and dried at 80° for 30 minutes in vacuo to yield 5 g of product. An analytical sample was recrystallized from acetone. λ Max: pH 1.7 290; pH 11 296 n.m. Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.5; H, 4.68; N, 17.7. Found: C, 50.98; 4.02; N, 17.48.

Preparation of 2,4-Dimethoxy-5-nitropyrimidine (I-13)

To methanol (50 ml) sodium was carefully added and allowed to react. To the resulting solution was added 2,4-dichloro-5-nitropyrimidine (5 g). The mixture was allowed to reflux for 1 hour. The solution was then neutralized to pH 6 with concentrated hydrochloric acid and then evaporated to dryness. The residue was suspended in hot water (50ml), filtered and then dried to air. Recrystallization was from petroleum ether to give an analytical product, λMax: pH 1.7 258 and pH 260 n.m. Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.3; H, 4.5; N 21.1. Found: C, 42.5; H, 4.6; N, 21.09.

Reaction of 2,4-Dimethoxy-5-nitro-6-ethoxalylmethylpyrimidine with Hydrochloric Acid (I-39)

To 300 ml of concentrated hydrochloric acid was added 2,4-dimethoxy-5-nitro-6-ethoxalylmethylpyrimidine (5.3 g) and allowed to react at 75°C for 3 hours. A precipitate which separated from the hydrocloric acid was filtered and then washed with water (25 ml). The reaction gave 2.3 g of the product which melted between temperatures of 190-192°C, λ Max: pH 1.7,308,411 n.m., and pH 11, 310 and 411 n.m; IR: 3290 cm^{-1},3000 cm^{-1}, 285 cm^{-1}, 1705 cm^{-1} 1640 cm^{-1}, 1400 cm^{-1}, and 790 cm^{-1}; NMR: 5.5 singlet (2H) and 10.5

complex (3H); R_f: Solvent A, 0.15, and Solvent C, 0.62.

Reaction of -chlorotoluene with Methyl-5,7-dimethoxy-1,4,6-triazaindene-2-carboxylate (M-26)*

Methyl-5,7-dimethoxy-1,4,6-triazaindene-2-carboxylate* (1 g) was dissolved in 10 ml of N,N-dimethylacetamide. To the solution was added 1 g of -chlorotoluene. The mixture was refluxed for two hours and allowed to stir overnight (18 hours). Concentrated hydrochloric acid (5 ml) was added to the solution and the mixture was stirred at 100° for one hour. The solution was then added to 50 ml of distilled water. The gummy residue which separated was collected by decanting the aquenous phase. The residue was then dissolved in 30 ml of methanol and then filtered and dried in vacuo for 30 minutes at 80°C.

*2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine.

Reaction of 2,4-Dimethoxy-8-methoxycarbonyl-9-deazapurine with methyl iodide (I-40).

To a solution of 25 ml of N,N-dimethylforamide (DMF) containing 2,4-dimethoxy-8-ethoxycarbonyl-9-deazapurine (0.4 g) methyl iodide (1.2 g) was added. The solution was heated at 70°C for two hours during which a precipitate separated. The precipitate was filtered, washed with ether (25 ml) and dried to air to yield 0.3 g of white product, m.p. 360 (above); λ Max: pH 1.7 275 n.m. and pH 11 302 n.m. Anal. Calcd. for $C_9H_9N_3O_4 \cdot 3/2\ H_2O$: C, 43.2; H, 4.8; N, 16.8. Found: C, 44.2; H, 4.56; N, 16.4.

Hydrolysis 2,4-Dimethoxy-8-ethoxycarbonyl-9-deazapurine

2,4-dimethoxy-8-ethoxycarbonyl-9-deazapurine (2 g) was dissolved in hot hydrochloric acid. The mixture was refluxed

for two (2) hours during which time a precipitate formed. The brown precipitate was then filtered and washed with 50 ml of cold distilled water and dried under reduced pressure at 65°C for two hours to yield 1.0 grams, m.p. (above) 360 C; R_f: Solvent A, 0.40 and Solvent B, .44; λMax: pH 1.7 222, 274, 305 (s) n.m. and pH 11 230, 275, 297 (s) n.m. Method 2: (N-27).

Reduction of 3-(5-Nitro-6-uracilyl)-pyruvic acid with Sodium Hydroxulfite (I-40).

Recrystallized 3-(5-nitro-6-uraclyl)-pyruvic acid (0.5 g) was allowed to react with sodium hydrosulfite (0.7 g) in methanolic potassium hydroxide (5% solution) overnight (18 hours) at room temperature A brown precipitate (0 38 g) separated and was washed with (25 ml) water The solid was stirred with methanol, and then recrystallized from acetone-water, m.p. 360 (above). IR: 3750 cm^{-1}, 3000 cm^{-1}, 1700 cm^{-1}, 1400 cm^{-1}, 1250 cm^{-1}, and 780 cm^{-1}; UV: λ-max pH 11 305, pH 1.7 305, R_f: Solvent A, 0.77; H, 4.8; N, 16.8. Found: C, 44.2; H, 4.56; N, 16.4.

Reaction of 2,6-dimethoxy-8-ethoxycarbonyl-9-deazapurine with chloropropene (I-72).

In aqueous potassium hydroxide (25 ml), 2,6-dimethoxy-8-ethoxy-carbonyl-9-deazapurine (1.6 g) was allowed to react with chloropropene (1.8 g) for 2 hrs. The solution was neutralized with cold dilute hydrochloric acid, evaporated to dryness and extracted with methylene chloride (35 ml). The solution was filtered and the solvent was removed under reduced pressure. The residue exhibited λmax, pH 11 277 n.m; pH 1.7 292 n.m. Infrared: 2925 cm^{-1}. Bands in the N-H and -C-regions were absent. The product was homogeneous in Solvent C: R_f: 0.71 m.p.

Reaction of 2,6-dimethoxy-8-ethoxycarbonyl-9-deazapurine with chlorotoluene (I-71).

To 20 ml of aqueous potassium hydroxide (five per cent), 2,6-dimethoxy 8-methoxycarbonyl-9-deazapurine (1.2 g) was dissolved and allowed to stir with α-chlorotoluene (1.3 g) for 2 hrs. The solution was neutralized with cold dilute hydrocloric acid and evaporated to dryness. The residue was then extracted with methylene chloride filtered, and again evaporated to dryness. The product showed λmax, pH 11 282 n.m.; pH 1.7 296 n.m. Infrared: 2925 cm^{-1}. Bands in the N-H and -C- regions were absent. The product appeared homogeneous in Solvent C: R_f: 0.78.

Methylation of 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (I-74).

Methyl Iodide (1.5 g) was added to 25 ml solution of 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (1.0 g) in aqueous potassium hydroxide (five per cent) and permitted to stir for 2 hours. The solution was neutralized with cold dilute hydrochloric acid and evaporated to dryness. The residue was extracted with methylene chloride filtered and evaporated to dryness. The product (0.8 g) exhibited λmax, pH 11 275 n.m; pH 1.7 290 n.m. Infrared: 2925 cm^{-1}. The product appeared pure in two solvent systems (A and C). Solvent A: R_f: 0.68, Solvent C: R_f: 0.70 m.p. 239-241.

Reaction of 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine with ammonia at elevated pressure (I-75).

Using a parr pressure reaction vessel, 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (0.58 g) was dissolved in 100 ml

of absolute methanol. Liquid ammonia was then added until the total volume reached 150 ml of solution. The solution was then allowed to react at 100°C and 150 psi for one hour. The solution was permitted to cool to room temperature and evaporated to dryness. The product showed λmax, pH 11 289 n.m.; pH 1.7 292 n.m. Infrared: 1690 cm^{-1} and many strong bands in the fingerprint region m.p. 162-165.

Reaction of 2,4-dimethoxy 5-nitro-6-methoxalymethylpyrimidine with ammonia at elevated temperature (I-77).

In a pressure reaction vessel (Parr Instruments) 60 ml of liquid ammonia was in-roduced and allowed to stand for five minutes. In 60 ml of absolute methanol, 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (0.9 g) was dissolved and added to the reaction vessel. The solution was then permitted to react for two and one-half hours at 100°C and 200 psi. The solution was allowed to cool to room temperature and was evaporated to dryness. The product (0.71 g) exhibited λmax, pH 11 300 n.m.; pH 1.7 292 n.m. product was heterogeneous in Solvent C. R_f: 0.04; R_f: 0.55. M.P. 183-185.

Reaction of 2,4-dimethoxy-5-nitro-6methylpyrimidine with methyl benzoate (I-37)

To 200 ml of metallic sodium (2 g) was added in a dry environment. Then methyl benzoate (7.0 g) was added and allowed to stir for fifteen minutes. The pH of the solution was checked to insure basicity. Then 2,4-dimethoxy-5-nitro-6-methylpyrimidine (7.5 g) was added and allowed to reflux for 24 hours. The solution was neutralized with cold concentrated hydrochloric acid and evaporated to dryness. The residue was washed with water, then with

petroleum ether and allowed to dry to air. The product (6.7 g) exhibited λmax, pH 11 338 n.m.; pH 1.7 340 n.m. Infrared; 2930 cm^{-1}, 1698 cm^{-1}. NMR: 5.6 singlet; 6.3 singlet; M.P. 240°.

Reaction of 2,4-Dimethoxy-5-nitro-6-methoxalylmethylpyrimidine with 2-Fluorobenzylchloride (I-95)

To 30 ml of abs. methanol 1.0 g of metallic sodium was added. Then 1.5 g of diethyloxalate and 2.2 g of 2,4-dimethoxy 5-nitro-6methylpyrimidine were added respectively and refluxed for 2 hours. A yellow precipitate formed which was filtered and washed with excess methanol. The precipitate formed which was filtered and washed with excess methanol. The precipitate (2.0 g) was collected and suspended in 250 ml of abs. methanol with 2-1fuorobenzylchloride (2.5g) and allowed to reflux for 9 hours. The solution was filtered (routinely) and brought to dryness. The residue was washed with 100 ml of methylene chloride, filtered and dried in vacuo at 70°C to yield 0.4 g. M.P. 223 (with decomposition). Recrystallization from methanol gave an analytical sample. UV. λ max pH 11 225 and 335 (s) n.m.; pH 1.7 263 and 345 (s) n.m.

Reaction of 2,6-Dimethoxy-8-methoxycarbonly-9-deazapurine with 3-Chlorobenzylchloride (M-30)

To 75 ml of N,N'-dimethylformamide 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (1.0 g) was added. Then potassium carbonate (0.9 g) and 3-chlorobenzylchloride (1.0g) were added to the solution. The mixture was heated at 60-70°C for 16 hours. The mixture was filtered and the filtrate was evaporated to a gum. The gum-like residue was crystallized from 20 ml of 95% methanol-water solution to give 0.6 g of product. max: pH 11 282 and 330 (s) n.m.; pH 1.7 293 n.m. M.P. 283° (decomposition).

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with Glycidol (I-84)

In 75 ml of N,N' dimethylformamide (DMF) 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (1.0 g) was dissolved. To this solution 0.9 g of potassium carbonate and 1.0 g of glycidol were added. The mixture was stirred for 16 hours at 60-70°C. The mixture was filtered and the filtrate evaporated to near dryness and slurred with 20 ml of methanol. The product isolated (0.2 g) exhibited λmax: pH 291 and 305 (s) n.m.; pH 1.7 291 n.m. M.P. 160-164°C. R_f: Solvent A:0.001 and B: 0.93.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with 4-Fluorobenzylchloride (M-29)

2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (1.0 g) was dissolved in 75 ml of N,N'-dimethylformamide (DMF). Potassium carbonate (0.9 g) and 4-fluorobenzylchloride (1.0 g) were added and the resulting mixture was stirred at 60-70°C for 16 hours. The mixture was filtered and the filtrate was evaporated to an oil and crystallized from 20 ml 95% methanol-water solution yielding 0.4 g of product. U.V.: λmax: pH 284, and 335 (s) n.m.; pH 1.7 292 n.m. M.P. 184-187.

Reaction of 2,4-Dimethoxy-5-nitro-6-methoxyalylmethylpyrimidine with Diethylamine (I-85)

A mixture of 2,4-dimethoxy-5-nitro-6-methoxalylmethyl-pyrimidine (1.0 g) and diethyl amine (1.0 g) in 75 ml of abs. methanol was refluxed for 16 hours. (As the reaction proceeded, the suspended material slowly dissolved). The solution was then filtered, evaporated to dryness and washed with excess ligroine. Recrystallization form 25 ml acetone gave 0.6 g of homogeneous product. U.V.: max: pH 11 262, 350 n.m.; pH 1.7 261 and 300 n.m;

pH 1.7 261 and 300 n.m. Infrared: 3000cm^{-1}, 1720cm^{-1}, 1050cm^{-1}.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with 4-Bromobenzylchloride (I-94)

2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine (1.0g) was dissolved in 75 ml of N,N' dimethylformamide (DMF) and potassium carbonate (0.9 g) was added. To this mixture 1.0 g of 4-bromobenxy-lchloride was added and allowed to stir at 60-70°C for 16 hours. The mixture was filtered and the solvent evaporated to near dryness. The gum was they crystallized form 20 ml of methanol-water solution to yield 0.4 g of product. U.V.: λmax: pH 11 282 and 332 n.m.; pH 1.7 291 n.m. Infrared: 2950cm^{-1}, 171cm^{-1}, 1050cm^{-1}. R_f: Solvent A: 0.88 and B: 0.91.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with 2,6-Dichlorobenzylchloride (I-91)

To 100 ml of N,N' dimethylformamide (DMF) 2,6-dimethoxy-8-methoxycarbonyl-9-deazapurine (2.2 g) was added. To this solution potassium carbonate (2.0 g) was suspended. Then to this mixture 2,6-dichlorobenzychloride (2.2 g) was added and permitted to heat between 60-70°C for 16 hours. The substance was filtered and evaporated to an oil. The oil was than crystallized from 20 ml of 95% methanol-water yielding 0.6 g. The product exhibited λmax: pH 11 284 and 330 n.m.; pH 1.7 290 n.m. Infrared: 2950cm^{-1}, 1710cm^{-1}, 1050cm^{-1}. The product appeared homogeneous in two solvent systems: A, 86 and B, 0.90.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with 2-Fluorobenzylchloride (I-93)

In 75 ml of N,N' dimethylformamide (DMF) was added 1.0g of

2,6-dimethoxy 8-methoxycarbonyl-9-deazapurine. Potassium carbonate (0.9 g) was then suspended and the resulting suspension stirred at 60-70°C with 1.0 g of 20-fluorobenzylchloride for 16 hours. The mixture was filtered and the solvent was then removed in vacuo and the resulting oil was crystallized form a 95% methanol-water solution to give 0.4 g of product. The product showed λmax: pH 11 285 and 333 n.m.; pH 1.7 292 n.m. Infrared: 2950cm^{-1}, 1710cm^{-1}, and 750cm^{-1}. R_f: Solvent A: .88 and B: 0.90.

Reaction of 2,4-Dimethoxy-5-nitro-6-methylpyrimidine with Ethyl cyanoacetate (I-86)

Metallic sodium (0.5 g) was added to 75 ml of abs. methanol. To the solution was added 2.0 g of ethyl cyanoacetate, followed by the addition of 2,4-dimethoxy-5-nitro-6-mehtylpyrimidine (2.0 g). The mixture was refluxed for 24 hours. The solution was neutralized with conc. hydrochloric acid and evaporated to to near dryness and treated with 35 ml of acetone.

Preparation of 1-(5-Nitro-6-uracilyl)-2-phenylethenes.

5-Nitro-6-methyluracil was added to a solution containing the aromatic aldehyde (10% molar excess) in pyridine (10 ml per gram of pyrimidine). The resulting solution was refluxed for 24 hours, and then the solution was evaporated to dryness at 65-70° in vacuo. Hot methanol (25 ml per gram of pyrimidine) was added to the residue, and after stirring, filtered and dried to air. The product was reprecipitated from dilute potassium hydroxide (1%), and dried in a vacuum oven for two hours at 80°C. (See Table II, Page 8)

Preparation of 1-(5-Nitro-6-uracilyl)-2-phenylethyne (N-19).

1-(or 2)-bromo-1-(or-2)-methoxy-1-(5-nitro-6-uracilyl)-2-phenylethyne (5 g) was dissolved in 95 ml of methanol con-

taining potassium hydroxide (5 g). The resulting solution was refluxed for 24 hours, during which time a precipitate formed. The precipitate formed was filtered and dried to air. The infrared spectra showed a sharp peak at 4.5 cm^{-1}. The product was then dissolved in water (50 ml), and neutralized at pH-. 5-6 with Dowex 50w -x 8 acid exchange resin. The precipitate which formed after neutralization was filtered and dried in a vacuum oven for two hours at 80°C to yield 4.5 g (75% yield) pf product, m.p. 198-200°C. R_f: Solvnet A.77; B .71; max, pH 11 227, λ max pH 11 275 and 340 n.m.; pH 1.7 235 and 320 n.m.

1-(5-Amino-6-uracilyl)-2-phenylethyne (N-30).

1-(5-Nitro-6-uracilyl)-2-phenylethyne (1 g) was suspended in water (20 ml). Sodium hydrosulfite (2 g) was then added and the mixture was stirred at room temperature for two hours. The mixture was then heated for 30 minutes to dissolve the solid then routinely filtered, and cooled to 25°C. The resulting solution was then reprecipitated by the addition methanol (20 ml) to yield 0.5 grams of product, λmax: pH 11 225, 272 n.m and pH 1.7 230, 270 n.m. The product was futher purefied by reprecipitation from water with methanol.

5-Amino-6-styryluracil (N-66).

5-nitro-6-styryluracil (10 g) was dissolved in dilute potassium hydroxide (5%) (200 ml). To the solution was added at 70° sodium hydrosulfite (10 g), and the resulting solution was stirred at 90°C for 30 minutes. The solution was then acidified at pH 6 with acetic acid, and cooled to 10°C. The precipitate which formed was filtered and washed with cold water

(100 ml) to yield 5 g of crude product, m.p. 278-280°C. λ max, pH 11 295 and 310 n.m.; pH 1.7 292 and 310 n.m.

1 or 2-bromo, 1 or 2-methoxy-1-(5-amino-6-uracilyl)-2-phenyl-ethane (N-67).

Bromine (2 g) was added to methanol (50 ml) while stirring at 55°C. 5-Amino-6-styryluracil (2 g) was then added to the resulting solution and the mixture was stirred at 55°C for thirty minutes. Additional bromine (2 g) was added and stirring was continued for 30 minutes. The solution was then evaporated to dryness in vacuo at 60°. Water (50 ml) was added to the residue which was then basified with dilute ammonium hydroxide (5%). The crude product was filtered and dried in a vacuum oven at 80°C for 15 minutes to yield 2.1 g of product, n.m.; pH 1.7 215 and 292 n.m.

1-(5-amino-6-uracilyl)-2-phenylethyne (N-68).

1 or 2-bromo, 1 or 2-methoxy-1-(5-amino-6-uracilyl)-2-phenyl-ethane (2 g) was dissolved in alcoholic potassium hydroxide (5%) (50 ml). The resulting solution was refluxed for 24 hours. The precipitate which formed was filtered and dried to air. The product did not give evidence of a triple bond and was not characterized further. The filtrate was evaporated to dryness to yield 1.5 grams of product, m.p.; pH1.7 276 n.m. The crude product which contained traces of starting material was stirred in water (20 ml), and neutralized with concentrated hydrochloric acid. The precipitate which formed was filtered and dried in vacuum oven at 80°C for 30 minutes to yield 1 g of product.

Reaction of 5-amino-6-styryluracil with nitrous acid (method 1) (N-72).

5-amino-6-styryluracil (1.5g) was dissolved in cold dilute potassium hydroxide (5%) (20 ml). To this solution sodium nitrite (1.5 g) was added, and the resulting solution was added dropwise to dilute hydrochloric acid (10%) (50 ml) previously cooled to 20°C. The precipitate which formed while stirring for 30 minutes was filtered and dried to air to yield 1 g of product. R_f: Solvent A .72, B.52, λmax, pH 11 245, and 292 n.m.; pH 1.7 245 and 292 n.m.

(Method 2) (N-73).

5-amino-6-styryluracil (1 g) was added to concentrated sulfuric acid (25 ml) previously cooled at 5°C. Sodium nitrite (1 g) was added, and the resulting solution was stirred at 5°C for 30 minutes. The solution was then poured over ice (25 g). The precipitate which formed was filtered and dried to air to yield 1.2 g of product, m.p. 138-140°. R_f: Solvent A .72; B.56; λmax, pH 11 250 and 292 n.m.; pH 1.7 250 and 292 n.m.

1-(2,4-Dimethoxy-5-nitro-6-pyrimidyl)-2-(2-chlorophenyl) ethene (N-40).

2,4-Dimethoxy-5-nitro pyrimidine (5 g) was dissolved in a solution containing 2-chlorobenzaldehyde (15 g) in pyridine (31.2 ml). The resulting solution was refluxed for 24 hours and then evaporated to dryness at 60° in vacuo. A gummy residue was formed to yield 5.1 g of product. λ max pH 11 253 and 286 nm; pH 1.7 285 n.m. The product was used without further purification after repeated attempts failed to yield a crystalline solid.

1 or 2-bromo, 1 or 2-methoxy-1-(2,4-dimethoxy-5-nitro-6-pyrimidyl)-

2-(chlorophenyl) ethane (N-51).

Bromine (2.5 g) was added to methanol (50 ml) while stirring at 55°C. 1-(2,4-dimethoxy-5-nitro-6-uracilyl)-2-(2-chlorophenyl) ethene (2.5 g) was then added in small aliquots, and the mixture was stirred for 30 min. Additional bromine (10 g) was then added, and the solution was stirred for 30 min. and evaporated to dryness in vacuo at 60°. The gummy residue which formed was dried to air overnight to yield 5.1 g of crude-wet product. The product was dissolved in methanol (50 ml) by heating and cooled to 35°C. An insoluable residue was removed by filtration. The filtrate was evaporated to dryness in vacuo at 60° to yield 2.2 g of gummy product. λ max, pH 11 385 n.m.; pH 1.7 262 and 385 nm.

1-(2,4-dimethoxy-5-nitro-6-pyrimidyl-2-(2-chlorophenyl) ethyne (N-55).

1 or 2 bromo, 1 or 2-methoxy-1-(2,4-dimethoxy-5-nitro-6-pyrimidyl)-2-(2-chlorophenyl) ethane (2.2 g) was dissolved in dilute alcoholic potassium hydroxide (5%) (50 ml). The resulting solution was refluxed for 24 hours during which time a precipitate formed which was filtered and dried to air. This product did not show evidence of a triple bond. The filtrate was evaporated to dryness in vacuo at 60° to yield 3.2 g of gummy product which gave evidence of a triple bond. max, pH 227 n.m.; pH 1.7 256 n.m. The product was then stirred in cold water (30 ml). A portion of the porduct was insoluable in water. The insoluable product was filtered and dried to air. (This product did not show evidence of a triple bond). The filtrate was evaporated to dryness. The gum which resulted was suspended in water (10 ml), and neutralized with acetic acid. A precipitate formed which was filtered and dried to air.

1 or 2 bromo, 1 or 2-methoxy-1-(5-nitro-6-uracilyl)-2-(2-chlorophenyl) ethane.

Bromine (10 g) was added to methanol (100 ml). 1-(5-nitro-6-uracilyl)-2-(2-chlorophenyl) ethene (10 g) was added in small aliquots. The resulting mixture was stirred at 35°C for 30 minutes. Additional bromine (20 g) was added, and the resulting solution was stirred for 30 minutes and evaporated to dryness in vacuo at 60°. Water (100 ml) was added to the residue which was then basified with dilute ammonium hydroxide (5%), filtered, and dried in a vacuum oven at 80°C for 30 minutes to yield 12.5 g of product, m.p. 183-186°C. Solvent A .90; B .91. λ max: pH 11 226 and 282 n.m; pH 1.7 274 and 369 n.m.

1-(5-amino-6-uracilyl)-2-(2-chlorophenyl) ethene (K-228).

1-(5-nitro-6-uracilyl)-2-(2-chorophenyl) ethene (15 g) was suspended in dilute potassium hydroxide (5%) (600 ml) while heating at 75°C. Sodium hydrosulfite (45 g) was added slowly at 75-80°C, and the resulting mixture was heated at 75-80°C for 30 minutes. The mixture was then filtered and the precipitate washed with water (100 ml). The light yellow product was suspended in hot water (300 ml) at 95-100°C, and acidified at pH 4 with concentrated hydrochloric acid. The product was filtered, washed with water (300 ml), and dried in a vacuum oven at 82°C for 1 hour to yield 5 g of product. Two grams of the product was reprecipitated from 20 ml of concentrated sulfuric acid by the addition of ice-water (50 g) to yield 1.5 g of the sulfate salt, m.p. 338-340 dec. λ max: pH 11 275, 350 n.m.; pH 1.7 275 n.m. R_f: Solvent A: .90, B: .64.

Reaction of 1-(5-nitro-6-uracilyl)-2-phenylethyne with sodium hydrosulfite (K-236).

1-(5-Nitro-6-uracilyl)-2-phenylethyne (2 g) was dissolved in

dilute potassium hydroxide (5%) (25 ml) while heating at 65°C. Sodium hydrosulfite (4 g) was then added in small portions at a rate that the temperature did not exceed 70°C. The mixture was stirred at 70°C for 20 minutes during whihc time a precipitate separated. The precipitate was filtered from the hot solution and washed with water (5 ml), and acetone (20 ml) to yield .2 g of product which decomposed at 278-285. λ max: pH 11 275, 350 n.m., pH 1.7 317 n.m. R_f: Solvent A: .67; B: .30.

Bromination of 5-nitro-6-styryluracil (N-44).

Bromine (20 g) was added to acetic acid (200 ml) while stirring at 30°C. To the solution was added 5-nitro-6-styryluracil (20 g) and the resulting mixture was stirred at 30°C for 30 min. Additional bromine (80 g) was then added, and the resulting solution was allowed to continue stirring for 1.5 hours at 30°C. The solution was then evaporated to dryness in vacuo at 60°C. Water (200 ml) was added to the residue and the resulting solution basified to pH 9 with ammonium hydroxide (50%). The product was then filtered and dried to air to yield 24.3 g of crude product. Recrystallization from methanol (200 ml) gave 12.2 g of product. m.p. 186-188°C. λ max: pH 11 226, 282 n.m.; pH 1.7 228, 274, 369 n.m. R_f: Solvent A: .001; B:.50.

Anal. Calcd. for $C_{12}H_9N_3Br_2O_2$: C, 34.40; H, 2.15; N, 10.01. Found: C, 34.21; H, 2.82; N, 9.73.

1,2-Dibromo-1-(5-amino-6-uracilyl)-2-phenylethane (N-85).

1,2,-dibromo-1-(5-nitro-6-uracilyl)-2-phenylethane (10 g) was dissolved in methanol (100 ml). Raney Nickel (30 g) previously washed in mathanol was then added to the solution. The mixture was allowed to react in the hydrogenator under 30 lb. of pressure until no more hydorgen was absorbed. The resulting mix-

ture was then filtered and the Raney Nickel extracted three times with boiling methanol (300 ml). The extracts were then combined and finally evaporated to dryness in vacuo at 60° to yield 6.2 grams of product, m.p. 191-195°C. λ max, pH 11 306 n.m.; pH 1.7 225 and 260 n.m. R_f: solvent A: .50; B: 15, .001 .08.

Reaction of 1,2-Dibromo-1-(5-amino-6-uracilyl)-2-phenylethane with 10% alcoholic potassium hydroxide (N-104).

1,2-dibromo-1-(5-amino-6-uracily-2-phenylethane (4 g) was dissolved in alcoholic potassium hydroxide (25 g in 75 g of methanol). The resulting solution was refluxed for 3 hours and adjusted to pH 4 with hydrochloric acid. The precipitate which formed was filtered and then suspended in cold water (80 ml). The insoluble material filtered and dried to air to yield 1.1 g of product which did not decompose below 360°C. λ max: pH 11 235 306 n.m.; pH 1.7 233, 310 n.m. R_f: Solvent A: .87; B:70.

Reduction of 1-(5-Nitor-6-uracilyl)-2-phenylethyne (N-96).

1-(5-nitro-6-uracilyl)-2-phenylethyne (1 g) was dissolved in dilute alcoholic potassium hydroxide (5%) (25 ml). Raney Nickel (2.5 g) was then added, and the resulting mixture was refluxed for 2 hours. The mixture was then filtered. The filtrate was neutralized with conc. hydrochloric acid, the precipitate filtered, and dried in a vacuum oven at 80°C for 30 minutes to yield .8 grams of product, m.p. 208-210°C. λ max, pH 11 225, 290 n.m.; pH 1.7 225, 268 n.m. R_f: Solvent A: 0.001, .15, B: 0.001.

Bromination of 1-(5-amino-6-uracilyl)-2-phenylethene (94).

Bromine (3 g) was added to acetic acid (20 ml) while stirring at 30°C. To the solution was added 5-amino-6-styryl-uracil (3 g) and the mixture stirred for 30 minutes. Additional bromine (9 g) was added, and the resulting solution was stirred for 1.5 hours at 30°C. The solution was then evaporated to dryness. Water (25 ml) was added to the syrupy residue which was filtered and dried to yield 3.6 g of product. λ max: pH 11 225, 286 n.m.; pH 1.7 225 and 292 n.m. R_f: Solvent A: .20; B: 0.00.

1-(5-nitro-6-uracilyl)-2-phenylethyne Preparation (N-129).

1,2-dibromo-1-(5-nitro-6-uracilyl)-2-phenylethane (15 g) was dissolved in dilute alcholic potassium hydroxide (10 g in 190 ml of methanol). The resulting solution was refluxed for 3 hours. A precipitate formed which was filtered and suspended in cold water (10 ml). The insoluable material was filtered and dried to air. The product was finally reprecipitated from dilute potassium hydroxide (5%) (140 ml), filtered, adjusted to pH 4 with acetic acid and dried in a vacuum oven at 82°C for 30 minutes to yield 6.2 g of product, m.p. 206-207°C. The product showed evidence of a triple bond in the region 2200 cm^{-1}. λmax: pH 11 279 n.m.; pH 1.7 240, 315 n.m. R_f: Solvent A: .001; B: .22. Anal. Calcd. $C_{12}H_7N_3O_4 .H_2O$: C, 523; H, 3.27; N, 15.25. Found: C, 52.61; H, 3.39; N, 13.97.

1-(2,4-dimethoxy-5-nitro-6-pyrimidyl)-2-phenylethene Preparation

Benzaldehyde (3 g) was dissolved in 3% sodium methoxide (60 ml). 2,4-dimethoxy-5-nitro-6-methylpyrimidine (3g) was then added, and the resulting solution was resluxed for 1 hour. The precipitate which formed was filtered and suspended in cold

water (90 ml). The soluable material was filtered, heated to dissolve in water (90 ml), and adjusted to pH 7 with acetic acid. The precipitate which formed was filtered and dried in a vacuum oven at 82°C for 1 hour to yield 3.2 g of product, m.p. 273-276°C. λ max: pH 11 225, 284, 308 n.m.; pH 1.7 287, 327 n.m. R_f: Solvent A: 33; B: .26. Anal. Calcd. for $C_{14}H_{13}O_4N_3$ 3/2 H_2O: C, 53.50; H, 5.10; N, 13.35.35. Found: C,53.25; H, 5.36; N, 13.44.

Reaction of 1-(5-nitro-6-uracilyl)-2-phenylethyne with sodium sulfide (K-237).

1-(5-nitro-6-uracilyl)-2-phenylethyne (1 g) was dissolved in water (30 ml) containing sodium sodium sulfide. The mixture was heated at 65-70°C for 30 minutes, and the solution was adjusted to pH 6 with acetic acid. The precipitate which formed was filtered and washed with excess water to yield .18 g of product which darkens at 178-180°C. λ max: pH 11 299 n.m.; pH 1.7 310 n.m. R_f: Solvnet A: .65; B: .001, .62.

Diazotizaiton of 1-(5-amino-6-uracilyl)-2-(2-chlorophenyl) ethene (K-229).

1-(5-amino-6-uracilyl)-2-(2-chlorophenyl) ethene (2 g) was dissolved in concentrated sulfuric acid (20 ml). The solution was then cooled to 10-15°C and sodium nitrite (2 g) was then added in small portions. The mixture was allowed to stir 30 minutes at 10-15°C. The mixture was finally poured over ice-water (100 g) at a rate that the temperature did not exceed 10°C. The resulting precipitate was filtered and washed with water (100 ml) to yield 1.1 g of product which darkens at 208-211°C. λ max: pH 11240, 303 n.m. pH 1.7 238, 304 n.m. R_f: Solvent A: .86; B: .60.

The precipitate which formed was filtered and dried to air to yield 0.4 g of product. U.V. λ max pH 11 257 and 350 (s) n.m.; pH 1.7 260 and 335 (s). M.P. 175-178. I.R. 2275 and 720cm^{-1}.

1-(2,4-Dimethoxy-5-nitro-6-pyrimidyl)-2-(2,6-dichlorophenyl)-ethene (M-33).

2,6-Dichlorobenzaldhyde (7.5 g) was dissolved in 3% sodium methoxide (100 ml). To this solution was added 2,4-dimethoxy-6-nitro-6-methylpyrimidine (5 g). The solution was refluxed for 2 hours, filtered, and reprecipitate washed with methanol and dried in vacuo at 80 C for 1 hour to yield 6 g. The product was recrystallized form acetone and dried in vacuo. M. P. 240-242. λ max: pH 11 258, 315; max pH 1.7 268, 340 (s). R_f: Solvent A: .92; Solvent B; .74.

1,2-Dibromo-1-(2,4-dimethoxy-5-nitro-6-pyrimidyl)-2-(2,6-dichlorophenyl) ethane (M-34.

Bromine (4 g) was dissolved in acetic acid 40 ml. To this solution was added 1-(2,4-dimethoxy-5-nitro-6-pyrimidyl)-2-(2,6-dichlorophenyl) ethene (4 g). After 30 minutes of stirring at room temperature additional Bromine (4 g) was added. Stirring was continued for 1½ hours and after which the solution was evaporated to dryness, the residue in water (50 ml) was made basic (pH 8) with ammonium hydroxide. The precipitate was filtered and washed with distilled water and dried in vacuo at 80°C for 1 hour to yield 5.4 g. One gram of the product was recrystallized (methanol 20 ml). M.P. 183-187°C. λ max pH 11 302; max: pH 1.7 290. R_f: Solvent A: .94; Solvent B: 96.

1,2-Dibromo-1-(2,4-dimethoxy-5-amino-6-pyrimidyl)-2-(2,6-dichlorophenyl) ethane (M-35).

1,2-Dibromo-1-(2,4-dimethoxy-5-amino-6-pyrimidyl)-2-(2,6-dichlorophenyl) ethane (4 g) was dissolved methanol (200 ml) followed by the addition of methanol-washed Raney Nickel The reaction mixture was allowed to react in a hydrogenator under 40 psi of hydrogen until no further absorption of hydrogen was noted. The catalyst was removed by filtration and then extracted with hot methanol (50 ml). The combined filtrate and washing was evaporated to dryness to yield 2.6 g. The product was recrystallized from methanol. M.P. 161-164°C.

λmax: pH 11 300, 240; λmax: pH 1.7 300, 240 R_f: Solvent A: .87; Solvent B: .95.

Reaction of alcoholic potassium hydroxide with 1,2-Dibromo-1-2,3-dimethoxy-5-amino-6-pyrimidyl)-2-(4,6-dichlorophenyl) ethane (M-36).

1,2-Dibromo-1-(2,4-dimethoxy-5-amino-6-pyrimidyl)-2-(2,6-dichlorophenyl) ethane (1.3 g) was dissolved 5% alcholic potassium hydroxide (50 ml). This reaction mixtures wase stirred for three (3) hours under vigorous refluxing conditions and evaporated to dryness. The residue was slurred in distilled water, filtered and dried in vacuo to yield 0.9 g. M. P. 210-216°C. λmax: pH 11 302, 240; λmax: pH 1.7 302, 340. R_f: Solvent A .89; Solvent B .95.

Reduction of 2,4-Dimethoxy-5-nitro-6-methylpyrimidine (AA-26)

A mixture of 5.0 g 2,4-dimethoxy-5-nitro-6-methylpyrimidine and 4.0 g of 64% hydrazine were refluxed and stirred with a magnetic stirrer for 2 hours. The dark red solution turned brown as the reaction proceeded. The reaction mixture was cooled to room temperature, and the brown solid filtered as a gum. The solid was washed repeatedly with absolute methanol and air dried. The resulting solid weighed 2.84 g (84%), M.P. 198°-200°C (uncorr). The solid exhibited λ max: pH 1.7; (solvent B) 0.66.

Condensation of Phenylglyoxal with 2,4-dimethoxy-5-nitro-6-methyl pyrimidine

A mixture of 1.0 g of 2,4-dimethoxy-5-nitro-6-methylpyrimidine and 1.0 g sodium in 200 ml methanol (deep red solution) was stirred at room temperature 3 hours, then refluxed with stirring 1 hour. After cooling to room temperature the solution was evaporated to almost dryness. Upon the addition of 100 ml water and acidification with con. HCl, a dark gummy residue was obtained. The gummy residue was treated repeatedly with toulene and evaporated to get rid of acetone. Finally, the semi solid residue was precipitated from a toulene solution with heptane. The residue exhibited λ max: pH 11 250 n.m.; pH 1.7 257 n.m. Infrared: 1700 cm^{-1}. R_f: (Solvent A) 0.81; (Solvent B) 0.68.

Reaction of 2,4-Dimethoxy-5-amino-6-methylpyrimidine with phenylglyoxal (AA-29)

A mixture of 1.0 g 2,4-dimethoxy-5-amino-6-methylpyrimidine in methanol was stirred at room temperature. After 8 hours,

1.0 g sodium was added and the reaction mixture stirred at room temperature over night, then refluxed for 2 hours. The solvent was evaporated to dryness under vacuum, and the residue taken up in 10 ml of water. The water solution was acidified with con. HCl while cooling in an ice bath, then made alkaline by bubbling in ammonia. After evaporation the aqueous solution, the solid residue was dissolved in methanol and treated with carbon. The methanol was allowed to evaporate over night to afford a solid. The solid residue exhibited λ max: pH 225 n.m.; PH 1.7 235 n.m. R_f: (Solvent A) 0.81; (Solvent B) 0.72.

Reaction of the sodium salt of 2,4-dimethoxy-5-nitro-6-methoxalyl methylpyrimidine with 2,6-trichlorotoulene (M-64)

2,4-Dimethoxy-5-nitro-6-methoxalyl methylpyrimdine (10.0 g) was suspended in a freshly prepared solution of sodium methoxide (1.0 g of sodium in 100 ml of methanol). The 2,6-trichlorotoulene (10.0 g) was added to the mixture and then was allowed to reflux for 48 hours. The mixture was filtered and the precipitate washed with methanol. The combined filtrates were evaporated to dryness in vacuo. The residue was slurred in chloroform and filtered. The precipitate was washed with chloroform (80 ml) and dried @ 80°C in vacuo for 1 hr. to yield 4.5 g of product. The product exhibited λ max: pH 11 225 n.m., 340 n.m.; pH 1.7 245 n.m., 278 (s) n.m., 340 (s) n.m. Positive Halogen Test. Infrared: 1760 cm^{-1}. The product appeared pure in two solvents: Solvent A, R_f; .93, Solvent C, R_f; .74.

Reaction of 2,4-Dimethoxy-5-nitro-6-methoxalyl methylpyrimidine with sodium bisulfite (M-67)

2,4-Dimethoxy-5-nitro-6-methoxalylmethlpyrimidine (10.0 g) was suspended in solution of methanol (100 ml) and water (50 ml).

A prepared solution of sodium bisulfite, 10.0 g in 50 ml of were added to the said suspension at a temperature 60-75°C, and without additional heating, the resulting solution was stirred for 2 hours. The solution was then evaporated to near dryness at room temperature and suspended in hot methanol and filtered. The filtrate was then evaporated to an oily residue which was treated with 5% hydrochloric acid solution and the resulting mixture was filtered and the precipitate was washed with 50 ml of water to yield 1.8 g product which was homogeneous in Solvent R_f; .66, Solvnet A, R_f; .91. Infrared: 1750 cm^{-1} λ max. pH 11 230 n.m., 335 n.m ; pH 1.7 230 n.m., 340 (s).

Reaction of 2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine with diethanolamine

2,6-dimethoxy-8-methoxy carbonyl-9-deazapurine (I-38) (2 g) was dissolved in 25 ml of methanol and to this solution was added diethanolamine (2 g). This soulution was refluxed for sixteen (16) hours after which was filtered, and the filtrate concentrated to an oil. The oily residue was treated with 25 ml of water and the pH of the solution adjusted to 6.5 with hydrochloric acid. The resulting precipitate was washed with 25 ml of cold water to yield 1.2 g of product which exhibited Infrared 1760 cm^{-1}. U.V. λ max: pH 11 225 n.m., 298 n.m.; pH 1.7 230 n.m. Solvent C, R_f; .21 Solvent A, R_f; .83.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with n-propylamine (M-59)

2,6-Dimethoxy-8-methoxy carbonly-9-deazapurine (I-38) (5 g) was dissolved in methanol 100 ml, and to this solution was added n-propylamine (5 g). This solution was refluxed for sixteen hours after which the solution was routinely filtered, and the filtrate concen-

trated to an oil in vacuo. The oily residue was treated with 25 ml of water and the pH was adjusted to 6.5 with hydrochloric acid. The resulting precipitate was filtered and washed with water to yield 3.5 g of crude product which exhibited U.V. max: pH 11 230 n.m., exhibiting λ max: pH 11 225 n.m., 260 n.m.; pH 1.7 230 n.m., 255 n.m., 350 (s). Infrared 3600 cm^{-1}, 1750 cm^{-1}. Solvent A, R_f; .96, .88; Solvent C, R_f; .85.

Reaction of 2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine with 1-adamatanamine (M-63)

2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine (I-38) (2 g) was dissolved in 25 ml of methanol, and to this solution was added 1-adamatanamine (2 g). This solution was refluxed over a 16 hour period after which was filtered, and the filtrate concentrated. The residue was treated with water and the medium's pH was adjusted to 6.5 with hydrochloric acid. The resulting precipitate was filtered and washed with water (55 ml). The product exhibited U.V. λ max: pH 11 225 n.m., 295 n.m., pH 1.7 228 n.m., 230 n.m.. Infrared 2900 cm^{-1}. Solvent A, R_f; .83, .52; Solvent C, R_f; .50, .28.

Reaction of 2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurines with 2,6-trichlorotoulene (M-43)

2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine (20.0 g) was dissolved in dimethylformamide (150.0 ml), and to this solution was added 20 g of potassium carbonate and 20 g of 2,6-trichlorotoulene. The mixture was stirred for 24 hours between 70-80°C.

The product was then filtered and the filtrate concentrated under diminished pressure. The residue was first extracted with 50 ml of ether and the ether layer decanted, then extracted

with 100 ml of water after which was filtered. The precipitate was homogeneous in two solvents: R_f; Solvent C, .00; Solvent A, .86 λ max: chloroform 243 n.m., 280 n.m., 315 n.m.

Reaction of 2,4-Dimethoxy-5-nitro-6-methoxalylmethyl pyrimidine with p-toulene sulfonyldrazide (M-70)

2,4-Dimethoxy-5-nitro-6-methoxalylmethylpyrimidine (2.0 g) was suspended in methanol (100 ml), and to the (2.0 g) and pyridine (2.0 ml) respectively. After refluxing for 16 hours the solution was evaporated to near dryness and slurred with 25.0 ml of water. The water layer was then decanted and the residue was dissolved in acetone (25.0 ml). The acetone solution was then added to an equal volume of water and the resulting mixture was filtered to yield .8 g of product which exhibited U.V. λ max: pH 11 230, 285 n.m.; 1.7 233, 265 n.m.; R_f; Solvent A, .01, .97, Solvent C, .23, .51, .01

Reduction of methyl-α-hydroxyimino-B-(2,4-dimethoxy-5-nitro-6-pyrimidyl) pyruvate (M-66)

Methyl-α-hydroxyimino-B-6-nitro-6-pyrimidyl pyruvate (3.3g) was dissolved in 80 ml of methanol and placed into a reaction vessel followed by the addition of Raney nickel. The vessel was then subjected to a pressurized hydrogen atmosphere (35 PSI) and shaken vigorously for 16 hours. The mixture was then filtered and the filtrate evaporated to dryness in vacuo at 45°C. The product was recrystallized from methanol to yield 1.2 g of product λ max: pH 11 250 n.m., 290 n.m., 340 n.m.; pH 1.7 n.m.; 250 n.m., 290 n.m., 360 n.m., Infrared: 3500 cm^{-1}, 3300 cm^{-1}.

Reaction of Benzil with 2,4-dimethoxy-5-nitro-6-methylpyrimidine (M-68)

2,4-dimethoxy-5-nitro-6-methylpyrimidine (5 g) was dissolved in sodium methoxide, (1 g Na in 50 ml of methanol). Benzil (5 g)

was added and this medium was refluxed for [illegible] hours. This solution was then neutralized and concentrated [illegible] an oil. The oil was dissolved in ether and dried with calcium chloride after which the ether was evaporated off leaving an oily residue. The product, an oil exhibited U.V. λ max: pH 11 233, 255 n.m.; pH 1.7 228, 255 n.m.; R_f; Solvent A, .97, .36; Solvent C, .69, .83.

Reaction of 2,4-Dimethoxy-5-amino-6-methylpyrimidine with benzil (M-71)

2,4-Dimethoxy-5-amino-6-methylpyrimidine (5 g) was suspended in sodium methoxide (1 g of sodium in 100 ml of methanol). To this suspension was added 5 g of benzil, after which the reaction mixture was refluxed for 48 hours. This mixture was then neutralized with concentrated hydrochloric acid, filtered, and washed with water to yield 3.5 g of product exhibiting U.V. λ max: pH 11 225, 255 n.m.; pH 1.7 228, 265 n.m. R_f, Solvent A: .97; Solvent C: .53, .21.

The product was heterogeneous in Solvent A: R_f, .45, .29; Solvent C: R_f, .23.

Reaction of 2,4-Dimethoxy-5-nitro-6-methoxalylmethyl pyrimidine with hydroxalamine hydrochloride (M-65)

2,4-Dimethoxy-5-nitro-6-methoxalylmethylpyrimidine (10.0 g) was suspended in methanol (100 ml), and to the suspension was added hydroxalamine hydrochloride (10.0 g) followed by the addition pyridine (10.0 ml). After refluxing for 16 hours the solution was evaporated to near dryness in vacuo and slurred with 25.0 ml of water. The water layer was tehn decanted and the residue was dissolved in acetone (25.0 ml). The acetone solution was then added to an equal volume of water and the resulting mixture was filtered to yield 3.3 g of crude product exhibiting max: pH 11 .225 n.m., 260 n.m., 350

pH 1.7 230 n.m., 350 (s). Infrared 3600 cm^{-1}, 1750 cm^{-1}. Solvent A, R_f; .96; Solvent C, R_f; .85.

Reaction of 2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine with allylamine (M-60)

2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine (I-38) (5 g) was dissolved in 100 ml of methanol, and to this solution was added 5 g of allylamine. This solution was refluxed for sixteen hours then filtered and the filtrate concentrated to an oil. The oily residue was treated with 25 ml of water and the pH of the solution adjusted to 6.5 with hydrochloric acid. The resulting precipitate was washed with 25 ml of cold water to yield 2.1 g, U.V. λ max: pH 1.7 227 290 n.m.; pH 11 225, 292 n.m.; R_f; Solvent A, 9; Solvent C, .28

Reaction of 2,6-Dimethoxy-8-methoxy carbonyl-9-deazapurine with Benzylamine (M-57)

2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine (I-38) (2 g) was dissolved in 25 ml of methanol, and to this solution was added 2 g of Benzylamine. This solution was refluxed for sixteen hours then concentrated to an oil under reduced pressure at 60°C. The residue was then dissolved in water 25 ml and acidified to a pH 6.5. The resulting precipitate was washed with water (50 ml) and dried under diminished pressure at 80°C for 1 hr. The yield of the crude product .9 g produced the following data: U.V. λ max: pH 11 229 n.m., 325 n.m. pH 1.7 232 n.m., 331 n.m. R_f; Solvent A, .14, .46. Solvent C, .001 .333.

Reaction 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with dibutylamine (M-58)

2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine (I-38) (2 g) was

dissolved in 25 ml of methanol, and to this solution was added dibutylamine (2 g). This solution was refluxed for sixteen hours after which was routinely filtered, and the filtrate concentrated to an oil. The oily residue was treated with 25 ml of water and the pH adjusted to 6.5. The resulting precipitate was washed with 25 ml of cold water to yield .8 g of product, U.V., λmax: pH 11 228 n.m., R_f; Solvent A, .43, .59 Solvent C, .23, .36. 227 n.m., pH 11 292 n.m., 225 n.m., R_f; Solvent A, .90; Solvent C, .28.

Reaction of 2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine with butylamine (M-61)

2,6-Dimethoxy-8-methoxycarbonyl-9-deazapurine (I-38) (5 g) was dissolved in 100 ml of methanol, and to this solution was added butylamine (5 g). This solution was refluxed for sixteen hours after which was filtered and the filtrate concentrated. The residue was treated with 25 ml of water and the pH of the solution adjusted to 6.5 with hydrochloric acid. The resulting precipitate was washed with 55 ml of water to yield 1.5 g. The product was recrystallized from a mixture of methanol and water to yield 1.1 g., U.V. λmax: pH 11 230 n.m., 302 n.m.; pH 1.7 230 n.m., 292 n.m.; R_f; Solvent A, .92; Solvent C, .23.

Reaction of 1-(5-Diazouracilyl)-2-phenylethene with butylamine (Q-78)

1-(5-Diazouracilyl)-2-phenylethene (Q-76) (3 g) was added to fifty (50) ml of methanol. This mixture stirred for five minutes then n-butylamine (5 g) was added and stirring was continued fro 13 hours. This mixture was filtered and washed with excess water. The resulting material was suspended in thirty (30) ml of water and carefully neutralized with glacial acetic acid. This product was then filtered and washed with excess water yielding 1.1 g, U.V. max: pH 11 307 n.m.;(pH 1.7)

Preparation of 1-(5-nitro-6-uracilyl)-2-phenylethene (Q-64)

4-chlorobenzaldehyde (45 g) was added to 200 ml of pyridine. 5-nitro-6-methyluracil was then added (30 g) to the solution. The mixture then refluxed for 24 hours. The mixture was evaporated in vacuo. The resulting product was slurred in methanol (10 ml/1 g) and filtered. It was then slurred in hot water (10 ml/1 g) and washed with excess MeOH when filtered to yield: 36 g, U.V. λmax: pH 11 330, 302, 276 n.m.; pH 1.7, 341, 292 n.m. R_f; Solvent A, .92 and Solvent C, 11, .30.

Preparation of 1-(5-amino-6-uracilyl)-2-phenylethene (Q-65)

1-(Nitrouracilyl)-2-(4-chloro)phenylethene (50 g) was added to 5% KOH (200 ml). This mixture was heated to 75°C. 150 g of sodium hydrosulfite were gradually added to the solution such that the temperature would not exceed 80°C. This mixture was then stirred for 30 minutes. The resulting mixture was then filtered and dried to yield 2.4 g, U.V. λmax: pH 11, 285 n.m., pH 1.7 285 n.m. R_f; Solvent A, 65 and Solvent C, .07

Reaction of 1-5(5-diazo-6-uracilyl)-2-phenylethene with n-dibutylamine (Q-79)

1-(5-diazo-6-uracilyl)-2-phenylethene (3 g) was added to 50 ml of methanol and stirred for five (5) minutes. n-Dibutylamine (5 g) was then added. The mixture was allowed to stir for 1 hour. The mixture was filtered and washed with H_2O. It was then suspended in water and neutralized with glacial acetic acid. It was again filtered and washed with water to yield 3.5 g U. V. λmax: pH 1.7 230 n.m., pH 1.7, 220, 248 (s), 300 n.m.

(50) ml of methanol. This mixture stirred for five munutes, then n-butylamine (5 g) was added. The mixture was allowed to stir for 12 hours. After stirring it was filtered and washed with water. The product was suspended in H_2O and then carefully neutralized with glacial acetic acid. It was again filtered and washed with water to yield 1.1 g. U.V. λ max: pH 1.7, 248, 310 n.m.; pH 11, 307 n.m.

Reaction of 1-(5-diazo-6-uracilyl)-2-phenylethene with benzenethiol (Q-77)

1-(5-diazouracilyl)-2-phenylethene (3 g) was added to fifty (50) ml of methanol. This mixture stirred for five (5) minutes, afterwards benzenethiol (5 g) was added and the mixture was allowed to continue stirring for 12 hours then filtered and washed with excess water. U.V. λ max: pH 11 220, 306 n.m.; pH 1.7, 220, 306 n.m.; R_f; Solvent A, .6 1, and Solvent C, .7 6.

Reaction of 1-(5-Diazo-6-uracilyl)-2-phenylethene with ethonthiol (J-123)

1-(5-diazo-6-uracilyl)-2-phenylethene (Q-76) (1.5 g) was added to 50 ml of methanol and the mixture was stirred 5 minutes. Ethanethiol (3.0 g) was then added to the mixture and stirring was continued for 30 minutes. The suspension was then heated to 60-65° for 30 minutes, then colled to room temperature (60-61) and was then filtered, washed with a small amount of methanol and allowed to dry to air to yield 0.5 g of product. The filtrate was evaporated to near dryness and provided 0.8 g crude product, λ max: pH 1.7, 302; pH 11 302.

Reaction of 1-(5-diazo-6-uracilyl)-2-phenylethene with appropriate amines

1-(5-diazo-6-uracilyl)-2-phenylethene (3 g) was added to 50 ml of water. The mixture was allowed to stir five munutes.

The appropriate amine (5 g) was added and the mixture was allowed to stir for 3 hours. The mixture was then heated for 30 minutes, cooled to room temperature and neutralized to pH 5 with glacial acetic acid. The product was then filtered, washed with water, then methanol and finally dried to air.

	R*	R	max: pH 1.7	pH 11
Q-80	$\emptyset CH_2$	H	252 302	257 297
Q-81	$HO\text{-}CH_2CH_2\text{-}$	$HO\text{-}CH_2CH_2\text{-}$	315	315
Q-82	$CH_3CH_2CH_2$	H	310	252 290
Q-83	$CH_3(OH_2)5$	H	250 307	248 317

Solvent Systems:

A: 5N Acetic Acid/t-Butanol (7/3)

B: 5N Ammonium Hydroxide/t-Butanol(/3)

C: 5% Sodium Bicarbonate

All melting points were determined on a Fisher John Melting Apparatus and are uncorrect.